# Living with cracks: Damage and repair in human bone

Our bones are full of cracks, which form and grow as a result of daily loading activities. Bone is the major structural material in our bodies. Although weaker than many engineering materials, it has one trick that keeps it ahead — it can repair itself. Small cracks, which grow under cyclic stresses by the mechanism of fatigue, can be detected and removed before they become long enough to be dangerous. This article reviews the work that has been done to understand how cracks form and grow in bone, and how they can be detected and repaired in a timely manner. This is truly an interdisciplinary research field, requiring the close cooperation of materials scientists, biologists and engineers.

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Bone has evolved to provide us with structural support: it needs to be stiff and strong whilst being as light as possible. These days we can make materials with excellent structural properties, such as metals and fibre composites, but, if offered a set of replacement bones, I would still choose to keep the ones I've got. Bone has a property, which, up to now, we have not been able to build into artificial materials: it can repair itself. This is very useful — it means that our bones can operate under conditions of high loading, subjected to stresses and strains that cause damage, which, if not repaired, would lead to failure in a relatively short time. Engineers make use of the same philosophy in finite-life structures such as the fuselage of an aircraft — they know that cracks will form and grow as a result of the cyclic stresses during take off, landing, and other manoeuvres; these are known as fatigue cracks. They specify regular maintenance schedules that involve inspections to detect cracks so that material can be repaired or replaced.

We have suspected for some time that bone is doing the same thing, continuously checking for the presence of cracks and other types of damage to its structure, and deliberately replacing damaged regions with new material[1]. Living dangerously, but thereby obtaining an evolutionary advantage for the organism in the form of bones that are lighter, allowing ease of movement, and less massive, reducing the drain on the body's energy resources[2]. Evidence for this includes the behaviour of bones in which the repair process has been suppressed, by the use of drugs[3] or by genetic manipulation[4]; in these cases, although bones form and grow, they fail spontaneously due to accumulation of unrepaired damage. Even now there are many intriguing aspects of the process that are not understood. This is a truly interdisciplinary field, requiring three different types of expertise: biologists to investigate the cellular and biochemical responses of bone and relate these to the performance of the organism as a whole; materials scientists to understand bone's mechanical properties and how they are determined by its structure; and engineers to describe the body's mechanics and to model the dynamics of the damage/repair system.

The problem can be stated in terms of three research questions: (1) What is the nature of mechanical damage in bone? If left unchecked, how quickly will it grow to cause failure? (2) How does the body detect this damage? How does it decide when repair is necessary? (3) How is the repair carried out?

## REPAIR

In fact it is the last of these questions that was answered first, at least in part. We have known for some decades that bone is continually replacing itself, the primary bone with which we are born being gradually turned into secondary bone throughout our lives. After an initial spurt of modelling activity, driven by the need to change the shape and size of our bones as we grow, the total bone volume settles down to a constant value, but turnover continues at a rate of a few percent per year. This turnover is known as remodelling, and it is carried out by specialized groups of cells of two kinds: osteoclasts, which resorb bone by releasing a powerful acid and an enzyme, and osteoblasts, which make new bone. These cells combine to form a basic multicellular unit (BMU) — a cavity, about 200 μm in diameter, which moves along the length of the bone at a speed of about 40 μm per day (Fig. 1). The result is a new portion of bone, of circular cross section, known as an osteon. A similar process occurs in the spongy, cancellous bone found inside our joints and elsewhere, although in this case the BMUs work on the surfaces inside the cancellous tissue.

At first it was not realized that these BMUs had a repair function, beyond the obvious fact that, by replacing a volume of bone, they would be removing any damage that happened to be in it. It has taken a lot of careful histological analysis[5–7] and some reasoning based on the quantitative fatigue behaviour of the material[8] to demonstrate that the remodelling process is not random, but is, at least to some degree, targeted towards the removal of damaged areas[3]. Other repair mechanisms have been suggested[9], but the

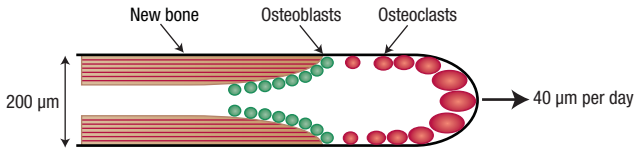


**Figure 1** Bone's repair mechanism. A BMU in which osteoclasts and osteoblasts work in sequence to eat away old and generate new bone.

current paradigm holds that BMUs are the primary way by which bone maintains its structural integrity.

## DAMAGE

To discuss the nature of damage in bone we first need to say something of its structure, which is summarized in Fig. 2. At the macroscopic scale bone comes in two forms. Compact (cortical) bone is essentially solid material, although spaces for blood vessels and living cells give it a porosity of about 5%; it makes up the majority of our long bones. Spongy cancellous bone is found inside bony structures, especially close to joints. It is essentially the same material as compact bone, but arranged in an open network to create a foam-like structure. At the microscopic scale both materials are made rather like plywood, from sheets of alternating lamellae that can be laid flat, or curved around in circles to protect blood vessels, forming osteons. Inside each lamella, at the ultrastructural level we find fibres of collagen, a soft, polymeric material made from long-chain molecules arranged in a triple helix, and crystals of hydroxyapatite (HA), a hard, brittle mineral material based on calcium. The ultrastructure is highly oriented, creating a strong anisotropy.

Mechanical loading creates damage; at the microscopic scale one can see small cracks that take the form of planar ellipses, typically having a major axis of length $2c = 400\,\mu m$ oriented approximately parallel to the bone's longitudinal axis, and a minor axis of length $2a = 100\,\mu m$. The observation of these cracks is greatly aided by the use of coloured dyes that are able to diffuse into the bone and chemically bind to exposed calcium[10]. These dyes have been improved in recent years and are now available in different colours[11], allowing cracks to be labelled at different times during an experiment[12]. This has yielded a great deal of information about how damage develops. Microcracks predominate in regions of compression — which constitutes the principal type of loading in our long bones — where they experience shear due to their orientation. In addition to these individual, linear cracks, areas called 'diffuse damage'[13] are also observed, which contain many small cracks, each

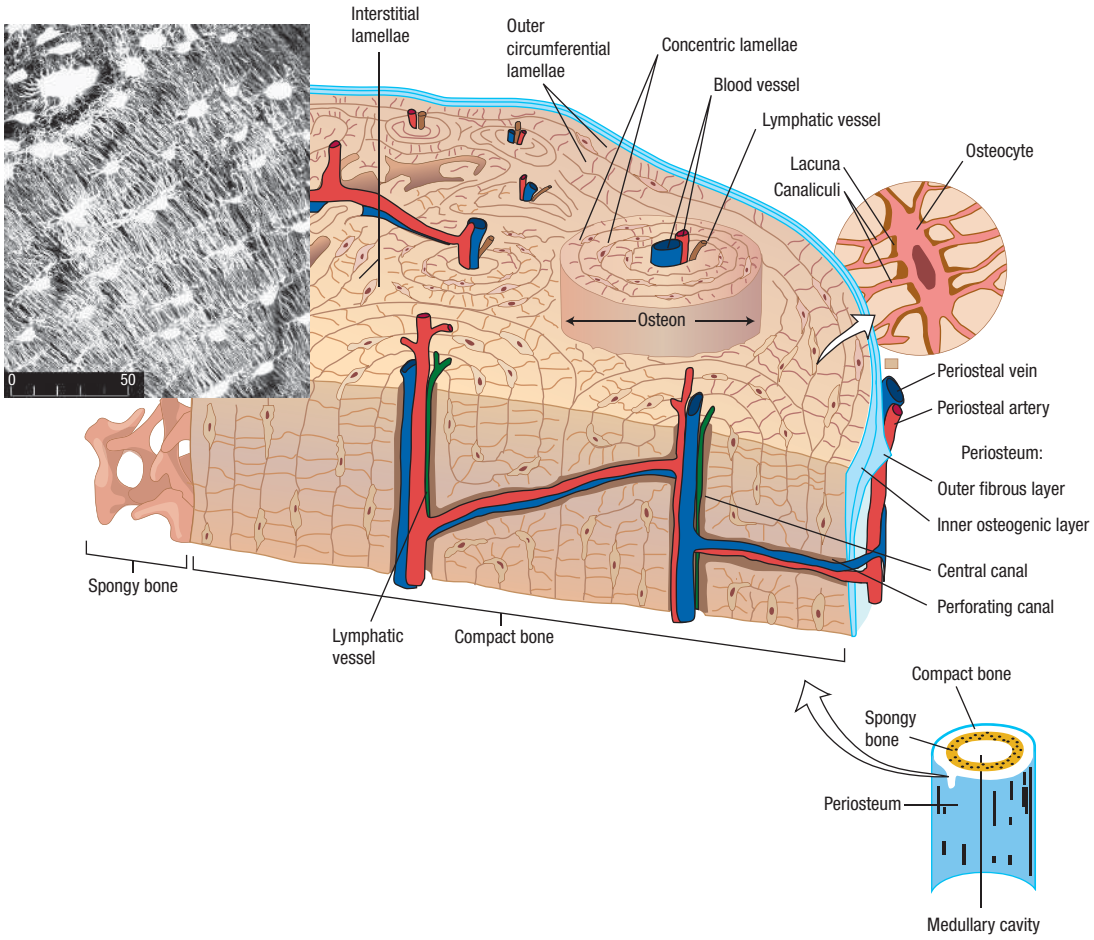


**Figure 2** The structure of bone. Colour schematic reprinted from ref. 66. Copyright (2002) Wiley. Black and white microscope image (scale bar in μm) showing osteocytes (white dots) linked by processes (fine white lines) forming the syncytium. Image reprinted from ref. 54. Copyright (2004) with permission from Elsevier.

of the order of a micrometre in size. Multiple cracks of intermediate size also occur, forming cross-hatched patterns[14]. Figure 3 shows examples of these various types of damage.

Histological studies have told us a lot about how this damage develops: chelating dyes can be administered *in vitro* and *in vivo*, allowing us to monitor the amount and type of damage in a laboratory specimen of dead bone, or in living animals while repair processes are operating. Other techniques are being developed, such as positron emission tomography[15,16], and new dyes may allow real-time imaging of microcracks in the body via scanning by computed tomography (CT) or magnetic resonance imaging (MRI)[17].

Currently the study of damage is a very active field; many experimental studies have been undertaken in recent years, showing, for example, that damage can be linked to reduced stiffness[18], to regions low in bone cells[19], to ageing in humans and animals[20–24] and to osteoporosis and its treatment[25]. Microcracking can also be found in the more calcified regions of cartilage and may be linked to osteoarthritis[26]. A lot of data is now appearing, along with some useful computer simulations[27,28], but currently we lack a clear theoretical perspective from which to view all this information.

## TOUGHNESS AND FATIGUE

Some cracks will be benign whilst others will threaten the integrity of the structure and so must be repaired: how can we tell which is which? This is the province of fracture mechanics, the science that studies cracks and how they grow in materials. We define a material property known as the fracture toughness, $K_c$, which tells us how tolerant a material is to the presence of cracks or, to put it another way, by how much a given crack will weaken the structure.

Like other composite materials, bone achieves a level of toughness that is much greater than that of its constituents — HA and collagen — and we have only recently begun to understand the mechanisms by which this toughness is achieved. Nalla and co-workers[29,30] and others[31] showed that $K_c$ is not constant but increases with crack length for cracks of the order of millimetres (Fig. 4a) — an important finding because the cracks in our bones rarely exceed this length. Nalla *et al.*[32] postulated that toughness in bone is achieved through bridging of the crack faces by unbroken ligaments of material (Fig. 4c), inhibiting further crack growth in the same way that reinforcing rods protect concrete. However, there are other possible mechanisms that may contribute, such as microcracking[32,33] bridging by collagen[34], and plasticity (which is the dominant source of toughness in metals). Currey[35] has shown how toughness and strength are juggled to allow bones to have special functions, such as the antlers of deer, which require high toughness and can tolerate low strength in order to get it.

Cracks can also grow very slowly, over long periods of time, even when their loading conditions are unchanged. Researchers studying the growth of microcracks[36,37] showed that, although a crack may initially grow quite quickly, its growth rate often declines to a minimum value, and indeed the crack may stop growing altogether (Fig. 5). This occurs when the crack meets up with features in the microstructure such as osteons or tubular canals. An example is shown in Fig. 3b where the left end of the crack has hit the outside of an osteon. Examination of microcracks formed *in vivo* or *in vitro* shows that most of them never grow beyond their first osteon[38].

These investigations have emphasized the importance of microstructure in preventing crack growth and thereby improving toughness and fatigue resistance, but ultrastructure is important too, as it determines the underlying mechanical properties of the material[39]. High strength, achieved via the HA crystals and their intimate bonding to the collagen around them, prevents the highly stressed material near the crack from failing. High stiffness is important too, because it reduces the amount of elastic strain energy, which is what a crack feeds on when it grows. A full picture on the role of ultrastructure has yet to emerge, but there have been several interesting observations published in recent years, in relation to the effects of ageing[29,40,41], gamma radiation[42] and varying levels of HA[43,44] and water[45]. What all this tells us is that bone cracking is a multiscale phenomenon that requires a hierarchical perspective, ranging from the molecular level up to the scale of the entire bone[46,47].

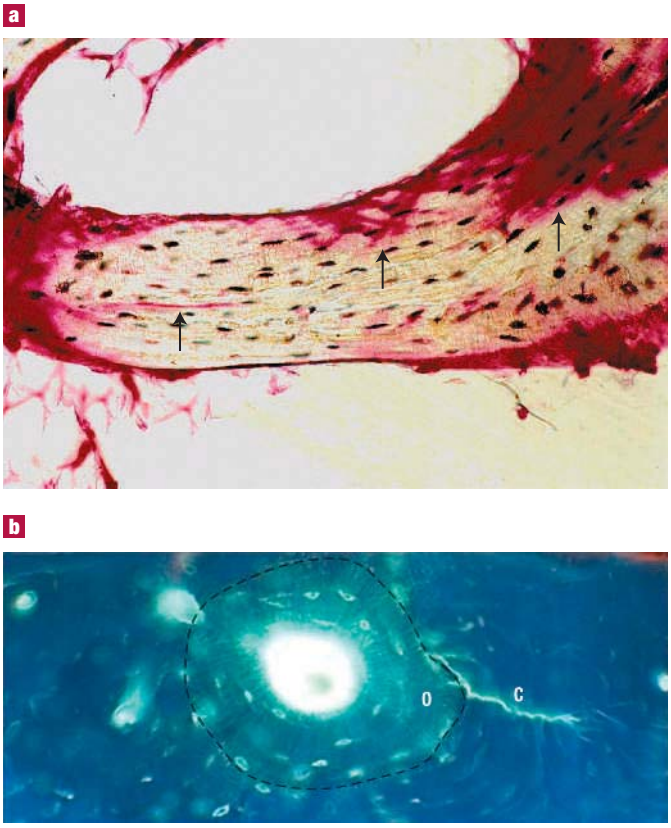


**Figure 3** Damage in bone. **a**, Cancellous bone showing examples of microdamage revealed by staining with basic fuschin (pink). The arrows indicate (from left to right): a microcrack (approximately 200 μm long), cross-hatching and diffuse damage respectively. Reprinted from ref. 23. Copyright (1998) with permission from Elsevier. **b**, A microcrack 'C' encounters an osteon 'O', and begins to grow around its cement line (dashed line). The microcrack is approximately 100 μm long. Reprinted from ref. 12. Copyright (2003) with permission from Elsevier.

## COMBINING DAMAGE AND REPAIR

We can think of living bones as a system of continual damage and repair, and this has inspired two very different lines of research. One line looks at the big picture, seeing bone as an example of a control system requiring feedback and stability — we will return to this research below. The other aims to understand the mechanisms by which bone detects the presence of cracks and decides whether or not to repair them. This is possibly the most challenging area and the one in which, despite some important recent work, there is still a lot to be done. The challenge is to understand the link between the mechanics of cracks and the biology of cellular behaviour. Attention has focused on the osteocytes — cells that live inside bone, contained

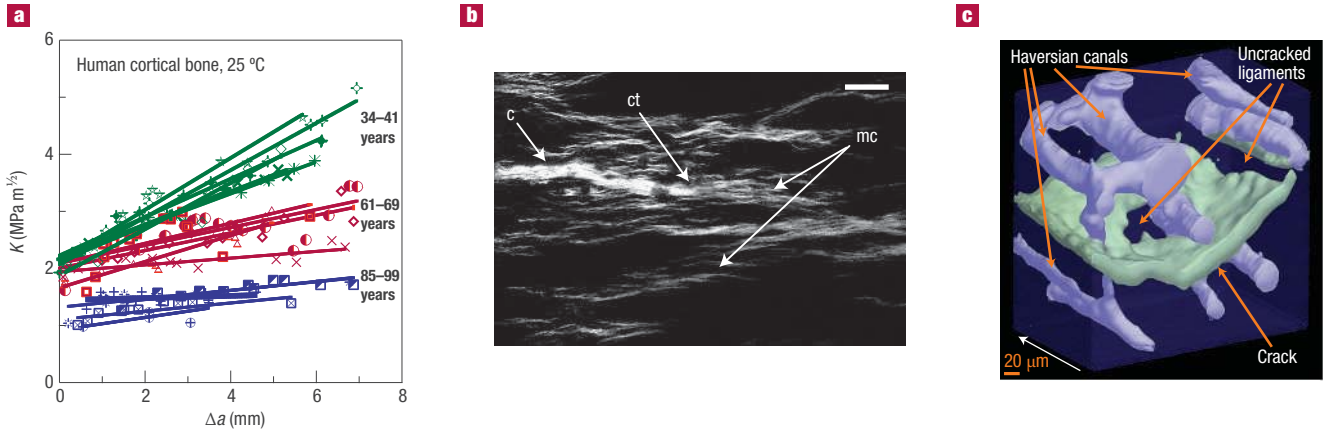


**Figure 4** Investigations of crack behaviour. **a**, Results from Nalla *et al.*[29] showing that crack extension ($\Delta a$) in the millimetre range requires increasing stress intensity ($K$), especially in bone from younger people. Copyright (2004) with permission from Elsevier. Possible toughening mechanisms include: **b**, microcracks 'mc' near the tip 'ct' of the crack 'c' (optical microscope image of bone stained with chelating dye; scale bar = 50 μm. From Zarrinkalam *et al.*[67], www.tandf.co.uk/journals); **c**, uncracked ligaments behind the crack tip (image obtained by Nalla *et al.*[30] using microtomography. Copyright (2005) with permission from Elsevier.

in small cavities and linked to their neighbours by extensions to the cell known as cellular processes. These processes meet at gap junctions, forming a network between osteocytes (Fig. 2) and bone lining cells that is reminiscent of that of the network of neurons in the brain[48]. This network, or 'syncytium' seems to be a means of intercommunication that can be used to detect and control the amount of damage in the surrounding bone.

Klein-Nulend and co-workers[49,50] have proposed a means by which BMUs could orient themselves to grow along a bone, or more specifically, parallel to the direction of principal stress. Fluid is continually flowing through the network of fine channels that contain the osteocytes, bringing essential nutrients. Using a computer simulation, they showed that flow rates are low in the region of bone immediately ahead of the BMU cavity[49,50]. Cells die in this stagnant area, possibly because they don't receive enough nutrients, but in the Klein–Nulend model, cell death is deliberate (apoptosis), triggered by a change in the level of nitric oxide released by cells, which acts as a signal indicating the rate of fluid flow. Osteoclasts are attracted to the apoptotic cells and so preferentially eat away the bone in this region.

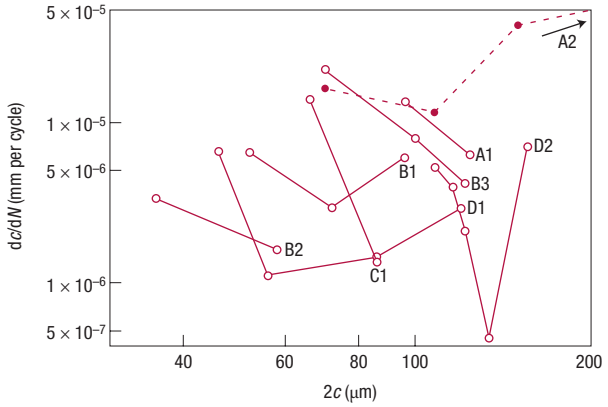


**Figure 5** Data from Akkus and Rimnac[37] showing the growth characteristics of various individual cracks (labelled A1, A2, B1, B2, B3, C1, D1, D2). The cyclic growth rate $dc/dN$ (change in crack half-length $c$ with number of cycles $N$) decelerates with crack length ($2c$) initially, often passing through a minimum value as the crack encounters a barrier to growth such as an osteon, as illustrated in Fig. 3b. Both scales are logarithmic. Reprinted from ref. 37. Copyright (2001), with permission from Elsevier.

This is a complex and elegant model, with elements of solid mechanics, fluid mechanics and biochemistry, and most of its steps have been demonstrated experimentally. However, it does not explain how BMUs can detect cracks. Cracks create regions of both high stress (near their tips) and low stress (along their sides) that cancel out, so that from a distance, a crack would be invisible to Klein–Nulend's BMU. However, cells do become apoptotic near cracks and regions of diffuse damage[51–53], where the osteocyte network becomes disrupted[54], possibly due to local changes in fluid flow. Other researchers have suggested various mechanisms by which dead or apoptotic cells could attract osteoclasts and thus initiate repair[55].

It has also been suggested that a crack could be detected as a result of the damage it causes to the network of cellular processes in canaliculi (small channels)[10]. We have recently investigated this mechanism in detail, using fracture-mechanics theory to show that cellular processes can be cut by the shear motions that occur across crack faces; the action is similar to that of a pair of scissors. We showed that the number of damaged processes varied significantly with both crack size and applied stress[56]. Microscopy demonstrated that these processes are indeed cut if the crack-face displacements are high enough[57]; current work is directed towards identifying the substances that are released by the broken processes and understanding how they are detected by osteoclast precursors, stimulating the formation of a BMU.

Other researchers don't worry about the mechanisms, but try to make models of the entire system, assuming that the amount of damage in a region of bone increases with time at a rate that depends on the local stress or strain: strain-energy density is often used as a parameter[27,58] because it is a simple scalar quantity. Repair is modelled as a decrease in the amount of damage, and a stable equilibrium is characterized by a balance between the rates of damage and repair[59]. This so-called 'damage mechanics' approach can be used in several ways. First, it can demonstrate the evolutionary advantages of living in a state of constant repair, allowing lighter, more delicate, gracile bones to be used than would be possible if damage never occurred[2]. Second, it can be

implemented in the form of a computer simulation, interfacing with other software such as finite element analysis: an entire bone can be modelled in all the complexity of its geometry and loading patterns. Surgical interventions such as the introduction of a hip-joint implant can be investigated[58], as can the effects of diseases such as osteoporosis. An advantage of this top-down approach is that we can include another important aspect of living bone, which is called functional adaptation. If bones are subjected to high levels of stress, or high numbers of cycles, to compensate they become thicker and stronger. Likewise, bones that are underused, due to periods of incapacity, become thin, porous and weak: this is known as 'disuse osteoporosis' and is one of the causes of fractures in elderly patients. The mechanisms by which bone recognizes these changes in its mechanical environment, and initiates adaptations, are just as poorly understood as the mechanisms by which it achieves repair, but it is very tempting to think that the two phenomena must be connected. For an engineer, the easiest way to optimise a design is to make the structure, use it, and see what happens, modifying your design in the light of experience. Perhaps bone is continually monitoring its state of damage and adjusting its architecture accordingly, the ideal state being not to have no damage, but to have just enough damage that can be repaired as you go along, ensuring a finite but acceptable risk of failure.

Two theoretical models have attempted to bridge the gap between the systems approach and the mechanistic approach. Martin has created computer simulations in which the number density of microcracks, and their repair by BMUs, are included[60,61]; this model has been used to investigate many interesting cases, such as the effects of anti-osteoporosis drugs that work by suppressing osteoclast activity[62]. It takes account of the fact that BMUs contribute to a bone's porosity, tending to increase stress and, with it, the rate of damage accumulation, creating a potential instability. This negative effect of the repair/remodelling process has been highlighted by some workers who believe that osteoporosis is caused by unnecessarily high levels of remodelling[63]. We developed a simulation that includes the growth-rate characteristics of short cracks (as shown in Fig. 5) as well as BMU behaviour, modelling every individual crack and BMU in a volume of bone using stochastic variables[28,64].

These models are capable of realistic predictions of the stable, equilibrium state of damage and repair, and of the instabilities that would lead to adaptation (for example, extra bone deposition) and, in extreme cases, to stress fractures. They can also be used to study other phenomena, such as the effect of bone size in different animals[65] and evolutionary development[2]. Large, multivariable simulations of this kind are difficult to set up and run stably, but they are probably an essential tool if we want to understand the behaviour of natural systems in all their complexity.

## CONCLUDING REMARKS

The fascinating study of bone damage and repair is clearly an activity that requires a multidisciplinary approach on many different fronts. In recent years we have seen some excellent progress. For example, we are now able to describe and quantify mechanical damage and to elucidate the mechanisms of cracking and toughness. A deeper understanding of these issues should not be too far away. Some more difficult parts of the puzzle are those that concern the responses of the living system. Although some pathways have been described whereby cells can detect strain and damage and initiate biochemical responses, the whole area of cell signalling is both complex and fascinating. Phenomena such as repair and remodelling are controlled not by a single biological system but by a variety of systems, working in parallel and probably interacting with each other. A major practical problem, in this as in other areas of bioengineering, is the provision of accurate experimental data. In many cases there is no alternative to the animal experiment, but great progress is being made in the development of cell cultures, which allow aspects of the living system to be studied in vitro.

The act of assembling the various pieces of this jigsaw is the business of those who make simulations of the whole system. With increasing computer power this activity is becoming more feasible: control theory could contribute greatly here. In the past we tended to view the human body as a complex engine — nowadays we can describe the workings of many parts of this engine, but we don't know how it is controlled. In the past few decades we have seen many examples of the life sciences and the physical sciences coming together to solve particular problems. In studying how bone becomes damaged and how it repairs itself, we are required to ask some very big questions; the answers to these questions have repercussions far beyond the particular topic that we are studying.

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## References


1. Martin, R. B. & Burr, D. B. A hypothetical mechanism for ths timulation of osteonal remodelling by fatigue damage. *J. Biomech.* **15,** 137–139 (1982).
2. Martin, R. B. Fatigue damage, remodeling, and the minimization of skeletal weight. *J. Theor. Biol.* **220,** 271–276 (2003).
3. Burr, D. B. Targeted and nontargeted remodeling. *Bone* **30,** 2–4 (2002).
4. Tsuji, K. *et al.* BMP2 activity, although dispensible for bone formation, is required for the initiation of fracture healing. *Nature Genet.* **38,** 1424–1429 (2006).
5. Burr, D. B. & Martin, B. R. Calculating the probability that microcracks initiate resorption spaces. *J. Biomech.* **26,** 613–616 (1993).
6. Mori, S. & Burr, D. B. Increased intracortical remodeling following fatigue damage. *Bone* **14,** 103–109 (1993).
7. Lee, T. C., Staines, A. & Taylor, D. Bone adaptation to load: Microdamage as a stimulus for bone remodelling. *J. Anat.* **201,** 437–446 (2002).
8. Taylor, D. Fatigue of bone and bones: An analysis based on stressed volume. *J. Orthop. Res.* **16,** 163–169 (1998).
9. Boyde, A. The real response of bone to exercise. *J. Anat.* **203,** 173–189 (2003).
10. Frost, H. M. Presence of microscopic cracks in vivo in bone. *Henry Ford Hosp. Med. Bull.* **8,** 25–35 (1960).
11. O'Brien, F., Taylor, D. & Lee, T. C. An improved labelling technique for monitoring microcrack growth in bone. *J. Biomech.* **35,** 523–526 (2002).
12. O'Brien, F. J., Taylor, D. & Lee, T. C. Microcrack accumulation at different intervals during fatigue testing of compact bone. *J. Biomech.* **36,** 973–980 (2003).
13. Vashishth, D. *et al.* In vivo diffuse damage in human vertebral trabecular bone. *Bone* **26,** 147–152 (2000).
14. Choi, K. & Goldstein, S. A. A comparison of the fatigue behaviour of human trabecular and cortical bone tissue. *J. Biomech.* **25,** 1371–1381 (1992).
15. Li, J., Miller, M. A., Hutchins, G. D. & Burr, D. B. Imaging bone microdamage in vivo with positron emission tomography. *Bone* **37,** 819–824 (2005).
16. Silva, M. J. *et al.* In vivo skeletal imaging of 18F-fluoride with positron emission tomography reveals damage- and time-dependent responses to fatigue loading in the rat ulna. *Bone* **39,** 229–236 (2006).
17. Lee, T. C. *et al.* Detecting microdamage in bone. *J. Anat.* **203,** 161–172 (2003).
18. Kawahara, D. & Murakami, T. Evaluation for mechanism of diffuse damage in cortical bone. *Trans. Jpn Soc. Mech. Eng. A* **71,** 936–943 (2005).
19. Qiu, S., Rao, D. S., Fyhrie, D. P., Palnitkar, S. & Parfitt, A. M. The morphological association between microcracks and osteocyte lacunae in human cortical bone. *Bone* **37,** 10–15 (2005).
20. Sobelman, O. S. *et al.* Do microcracks decrease or increase fatigue resistance in cortical bone? *J. Biomech.* **37,** 1295–1303 (2004).
21. Frank, J. D. *et al.* Aging and accumulation of microdamage in canine bone. *Bone* **30,** 201–206 (2002).
22. Schaffler, M. B., Choi, K. & Milgrom, C. Aging and matrix microdamage accumulation in human compact bone. *Bone* **17,** 521–525 (1995).
23. Fazzalari, N. L., Forwood, M. R., Smith, K., Manthey, B. A. & Herreen, P. Assessment of cancellous bone quality in severe osteoarthrosis: Bone mineral density, mechanics, and microdamage. *Bone* **22,** 381–388 (1998).
24. Mori, S., Harruff, R., Ambrosius, W. & Burr, D. B. Trabecular bone volume and microdamage accumulation in the femoral heads of women with and without femoral neck fractures. *Bone* **21,** 521–526 (1997).
25. Dai, R. C., Liao, E. Y., Yang, C., Wu, X. P. & Jiang, Y. Microcracks: An alternative index for evaluating bone biomechanical quality. *J. Bone Miner. Metab.* **22,** 215–223 (2004).
26. Muir, P. *et al.* Role of endochondral ossification of articular cartilage and functional adaptation of the subchondral plate in the development of fatigue microcracking of joints. *Bone* **38,** 342–349 (2006).
27. Huiskes, R., Rulmerman, R., Van Lenthe, G. H. & Janssen, J. D. Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. *Nature* **405,** 704–706 (2000).
28. Taylor, D. & Lee, T. C. Microdamage and mechanical behaviour: Predicting failure and remodelling in compact bone. *J. Anat.* **203,** 203–211 (2003).
29. Nalla, R. K., Kruzic, J. J., Kinney, J. H. & Ritchie, R. O. Effect of aging on the toughness of human cortical bone: Evaluation by R-curves. *Bone* **35,** 1240–1246 (2004).
30. Nalla, R. K., Kruzic, J. J., Kinney, J. H. & Ritchie, R. O. Mechanistic aspects of fracture and R-curve behavior in human cortical bone. *Biomaterials* **26,** 217–231 (2005).

31. Malik, C. L., Stover, S. M., Martin, R. B. & Gibeling, J. C. Equine cortical bone exhibits rising R-curve fracture mechanics. *J. Biomech.* **36,** 191–198 (2003).
32. Nalla, R. K., lken, J. S., Kinney, J. H. & Ritchie, R. O. Fracture in human cortical bone: Local fracture criteria and toughening mechanisms. *J. Biomech.* **38,** 1517–1525 (2005).
33. Vashishth, D., Tanner, K. E. & Bonfield, W. Experimental validation of a microcracking-based toughening mechanism for cortical bone. *J. Biomech.* **36,** 121–124 (2003).
34. Yeni, Y. N. & Fyhrie, D. P. A rate-dependent microcrack-bridging model that can explain the strain rate dependency of cortical bone apparent yield strength. *J. Biomech.* **36,** 1343–1353 (2003).
35. Currey, J. D. Mechanical properties of bone tissues with greatly differing functions. *J. Biomech.* **12,** 313–319 (1979).
36. Hazenberg, J. G., Taylor, D. & Lee, T. C. Mechanisms of short crack growth at constant stress in bone. *Biomaterials* **27,** 2114–2122 (2006).
37. Akkus, O. & Rimnac, C. M. Cortical bone tissue resists fatigue fracture by deceleration and arrest of microcrack growth. *J. Biomech.* **34,** 757–764 (2001).
38. O'Brien, F. J., Taylor, D. & Lee, T. C. The effect of bone microstructure on the initiation and growth of microcracks. *J. Orthop. Res.* **23,** 475–480 (2005).
39. Nyman, J. S., Reyes, M. & Wang, X. Effect of ultrastructural changes on the toughness of bone. *Micron* **36,** 566–582 (2005).
40. Wang, X., Xiaoe, L. I., Shen, X. & Agrawal, C. M. Age-related changes of noncalcified collagen in human cortical bone. *Ann. Biomed. Eng.* **31,** 1365–1371 (2003).
41. Zioupos, P., Currey, J. D. & Hamer, A. J. The role of collagen in the declining mechanical properties of aging human cortical bone. *J. Biomed. Mater. Res.* **45,** 108–116 (1999).
42. Mitchell, E. J., Stawarz, A. M., Kayacan, R. & Rimnac, C. M. The effect of gamma radiation sterilization on the fatigue crack propagation resistance of human cortical bone. *J. Bone Joint Surg. A* **86,** 2648–2657 (2004).
43. Currey, J. D. Effects of differences in mineralization on the mechanical properties of bone. *Phil. Trans. R. Soc. Lond. B* **304,** 509–518 (1984).
44. Wasserman, N., Yerramshetty, J. & Akkus, O. Microcracks colocalize within highly mineralized regions of cortical bone tissue. *Eur. J. Morphol.* **42,** 43–51 (2005).
45. Nyman, J. S. *et al.* The influence of water removal on the strength and toughness of cortical bone. *J. Biomech.* **39,** 931–938 (2006).
46. Akkus, O., Yeni, Y. N. & Wasserman, N. Fracture mechanics of cortical bone tissue: A hierarchical perspective. *Crit. Rev. Biomed. Eng.* **32,** 379–425 (2004).
47. Vashishth, D. Age-dependent biomechanical modifications in bone. *Crit. Rev. Eukar. Gene* **15,** 343–357 (2005).
48. Turner, C. H., Robling, A. G., Duncan, R. L. & Burr, D. B. Do bone cells behave like a neuronal network? *Calcified Tissue Int.* **70,** 435–442 (2002).
49. Burger, E. H., Klein-Nulend, J. & Smit, T. H. Strain-derived canalicular fluid flow regulates osteoclast activity in a remodelling osteon — a proposal. *J. Biomech.* **36,** 1453–1459 (2003).
50. Klein-Nulend, J., Bacabac, R. G. & Mullender, M. G. Mechanobiology of bone tissue. *Pathol. Biol.* **53,** 576–580 (2005).
51. Bentolila, V. *et al.* Intracortical remodeling in adult rat long bones after fatigue loading. *Bone* **23,** 275–281 (1998).
52. Noble, B., Alini, M. & Richards, R. G. Bone microdamage and cell apoptosis. *Eur. Cells Mater.* **6,** 46–55 (2003).
53. Noble, B. S. *et al.* Mechanical loading: Biphasic osteocyte survival and targeting of osteoclasts for bone destruction in rat cortical bone. *Am. J. Physiol. Cell Ph.* **284,** C934–C943 (2003).
54. Colopy, S. A. *et al.* Response of the osteocyte syncytium adjacent to and distant from linear microcracks during adaptation to cyclic fatigue loading. *Bone* **35,** 881–891 (2004).
55. Verborgt, O., Gibson, G. J. & Schaffler, M. B. Loss of osteocyte integrity in association with microdamage and bone remodeling after fatigue in vivo. *J. Bone Min. Res.* **15,** 60–67 (2000).
56. Taylor, D., Hazenberg, J. G. & Lee, T. C. The cellular transducer in damage-stimulated bone remodelling: A theoretical investigation using fracture mechanics. *J. Theor. Biol.* **225,** 65–75 (2003).
57. Hazenberg, J. G., Freeley, M., Foran, E., Lee, T. C. & Taylor, D. Microdamage: a cell transducing mechanism based on ruptured osteocyte processes. *J. Biomech.* **39,** 2096–2103 (2006).
58. Huiskes, R. in *Non-cemented Total Hip Arthroplasty* (ed. Fitzgerald, R.) 283–302 (Raven, New York, 1988).
59. Prendergast, P. J. & Taylor, D. Prediction of bone adaptation using damage accumulation. *J. Biomech.* **27,** 1067–1076 (1994).
60. Martin, B. Mathematical model for repair of fatigue damage and stress fracture in osteonal bone. *J. Orthop. Res.* **13,** 309–316 (1995).
61. Hazelwood, S. J., Martin, R. B., Rashid, M. M. & Rodrigo, J. J. A mechanistic model for internal bone remodeling exhibits different dynamic responses in disuse and overload. *J. Biomech.* **34,** 299–308 (2001).
62. Nyman, J. S., Yeh, O. C., Hazelwood, S. J. & Martin, R. B. A theoretical analysis of long-term bisphosphonate effects on trabecular bone volume and microdamage. *Bone* **35,** 296–305 (2004).
63. Heaney, R. P. Is the paradigm shifting? *Bone* **33,** 457–465 (2003).
64. Taylor, D. & Lee, T. C. A crack growth model for the simulation of fatigue in bone. *Int. J. Fatigue* **25,** 387–395 (2003).
65. Taylor, D. Scaling effects in the fatigue strength of bones from different animals. *J. Theor. Biol.* **206,** 299–306 (2000).
66. Tortora, G. J. *Principles of Human Anatomy* (Wiley, New York, 2002).
67. Zarrinkalam, K. H., Kuliwaba, J. S., Martin, R. B., Wallwork, M. A. B. & Fazzalari, N. L. New insights into the propagation of fatigue damage in cortical bone using confocal microscopy and chelating fluorochromes. *Eur. J. Morph.* **42,** 81–90 (2005).


## Competing financial interests

The authors declare no competing financial interests.