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Review article

Fatigue of mineralized tissues: Cortical bone and dentin

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ABSTRACT

Gaining a mechanistic understanding of the mechanical properties of mineralized tissues, such as dentin and cortical bone, is important from the perspective of developing a framework for predicting and preventing failure of teeth and whole bones, particularly with regard to understanding the effects of microstructural modifications from factors such as aging, disease, or medical treatments. Accordingly, considerable research efforts have been made to determine the specific mechanisms involved in the fatigue and fracture of mineralized tissues, and to discover how these mechanisms relate to features within the respective microstructures. This article seeks to review the progress that has been made specifically in the area of fatigue, focusing on the research that moves our understanding beyond simple fatigue life (S/N) concepts and instead addresses the separate mechanisms for microdamage initiation, crack propagation, and in the case of bone, repair and remodeling.

Contents

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1. Introduction

Maintaining the structural integrity of "hard" mineralized tissues, such as bone and dentin, is of great importance since these tissues make up the primary load bearing structures in the body. The importance of understanding the response of mineralized tissues to cyclically applied fatigue loading was recognized roughly half a century ago in the work of Evans and Lebow on human cortical bone (Evans and Lebow, 1957). This is because although most clinical human bone fractures are the result of a single overload, or dynamic, fracture event, there is clinical significance for fractures which occur over time (*i.e.*, stress fractures) as a result of periods of cyclic and/or sustained loading (Meurman and Elfving, 1980; Burr, 1997; Iwamoto and Takeda, 2003; Taylor, 2003). Stress fractures are a well recognized clinical problem with incidence rates of 1%–4% often being reported (Burr, 1997; Taylor, 2003), with even higher rates cited for adolescent athletes and military recruits (Meurman and Elfving, 1980; Iwamoto and Takeda, 2003; Taylor, 2003). They are commonly seen within a few weeks of a sudden systematic increase in the loading patterns experienced by the bone, when the time elapsed is insufficient for an adaptational response to alleviate the deleterious effects of the increased stress levels (Taylor, 2003). In addition, cyclic loading can be a factor in so-called "fragility" fractures commonly seen in the elderly, where there is increased fracture risk due to reduced bone quality as a result of osteoporosis (Taylor, 2003).

In teeth, cracked tooth syndrome, or incomplete fracture, has long been recognized as a significant clinical problem (Cameron, 1964), and it still receives much attention in the clinical dental literature, *e.g.*, Türp and Gobetti (1996), Ellis (2001), Lynch and McConnell (2002). The most common symptoms include tooth pain or discomfort during applied pressure or temperature change, and the tooth often will completely fracture after some time. This overall process of crack initiation (*i.e.*, the development of cracked tooth syndrome) followed by final growth to failure due to cyclic applied loading is what the engineering community routinely refers to as fatigue failure. Although an early study investigated the possibility of tooth fracture due to fatigue from thermal cycling (Brown et al., 1972), it is only relatively recently that investigations have focused on the fatigue of tooth tissues due to cyclic mechanical loading, as from masticatory stresses (Tonami and Takahashi, 1997; Arola et al., 2002; Arola and Rouland, 2003; Dong and Ruse, 2003; Nalla et al., 2003a, 2004a; Arola et al., 2005; Kinney et al., 2005; Kruzic et al., 2005; Arola and Reprogel, 2006; Bajaj et al., 2006; Kruzic and Ritchie, 2006).

Gaining a mechanistic understanding of the mechanical properties of mineralized tissues is important from the perspective of developing a framework for predicting and preventing failure, particularly with regard to understanding the effects of microstructural modifications from factors such as aging, disease, or medical treatments. With this goal in mind, the purpose of this article is to review the progress that has been made in understanding the mechanisms of fatigue failure in mineralized tissues and when possible to connect these mechanisms to the role of microstructure and potential methods for predicting fatigue failure.

2. The structure of dentin and cortical bone

Mineralized tissues such as bone and dentin are composed of the same basic building blocks, namely an organic matrix comprised mostly of type-I collagen, a mineral phase (calcium phosphate based apatite), and fluid, although the ratio of these components and the complexity of the microstructure they form can vary even for one type of tissue. Indeed, the composition, structure, and properties of bone vary with factors such as skeletal site, age, sex, physiological function and mechanical loading. On average though, the organic/mineral volume ratio in human cortical bone and human dentin are roughly 1:1 and 2:3, respectively.

The microstructure of dentin consists of apatite mineral distributed in the form of ~5 nm thick crystallites in a scaffold created by the collagen fibrils (50–100 nm diameter). The distinctive feature of the microstructure is the distribution of cylindrical tubules (1–2 μm diameter) that run from the soft, interior pulp to the dentin–enamel junction. These tubules are surrounded by a collar of highly mineralized peritubular dentin (~1 μm thick) and are embedded within a matrix of mineralized collagen, called intertubular dentin (Kinney et al., 2003). Conversely, the microstructure of cortical bone is hierarchical and more complex (Currey, 1982; Rho et al., 1998; Weiner and Wagner, 1998). At nanoscale dimensions, bone is composed of type-I mineralized collagen fibers (up to 15 μm in length, 50–70 nm in diameter) surrounded by, and impregnated with, carbonated apatite nanocrystals (tens of nm in length and width, 2–3 nm in thickness) (Rho et al., 1998). These fibers are further organized at microstructural length-scales into a lamellar structure with adjacent lamellae being 3–7 μm thick (Weiner and Wagner, 1998). Large vascular channels (up to 50–90 μm diameter) oriented roughly along the longitudinal direction of the bone and surrounded by circumferential lamellar rings form the secondary osteons (up to 200–300 μm diameter), with cement lines at the outer boundaries (Currey, 1982). As a structural material, bone is unique when compared to engineering materials, and even dentin, due to its well known capacity for self-repair and adaptation to changes in mechanical usage patterns, *e.g.*, Chamay and Tschantz (1972), Jones et al. (1977), Burr et al. (1985), Martin (2000), Burr (2002), Lee et al. (2002), Taylor (2003). This property of bone plays a significant role in its *in vivo* fatigue behavior.

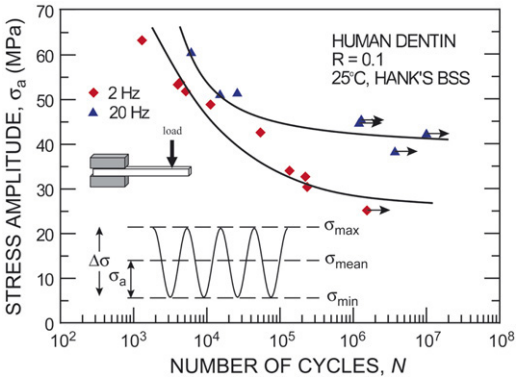

Fig. 1 – Traditional stress-life (S/N) fatigue data for human dentin at two different cyclic frequencies, tested in 25 °C Hanks' Balanced Salt Solution (HBSS) (Nalla et al., 2003a). Figure reproduced with permission from Kruzic and Ritchie (2006).

3. Fatigue life studies

One traditional method for quantitatively characterizing the fatigue behavior of a material is by measuring the total cycles to failure, N_f, as a function of the alternating stress amplitude, $\sigma_a = (\sigma_{max} - \sigma_{min})/2$, where σ_{max} and σ_{min} are the maximum and minimum stresses experienced during the loading cycle, respectively (Fig. 1 inset). This is termed the *stress-life* or "S/N" approach. This method utilizes nominally flaw-free, "smooth-bar", specimens loaded with prescribed stress levels. The measured fatigue lifetime represents the number of the cycles both to initiate and propagate a (dominant) crack to cause failure.[1] From a perspective of quantitatively assessing fatigue damage, the S/N approach is easy to apply experimentally, and consequently has received the most attention for characterizing the fatigue behavior of mineralized tissues, such as teeth and bone (Evans and Lebow, 1957; Swanson et al., 1971; Gray and Korbacher, 1974; Carter and Hayes, 1976; Carter et al., 1976; Lafferty and Raju, 1979; Carter and Caler, 1983; Caler and Carter, 1989; Choi and Goldstein, 1992; Zioupos et al., 1996a,b; Tonami and Takahashi, 1997; Currey, 1998; Vashishth et al., 2001; Zioupos et al., 2001; Nalla et al., 2003a; Taylor et al., 2003; Nalla et al., 2004a; Kinney et al., 2005; Arola and Reprogel, 2006). In general, mineralized tissues display S/N curves similar to ductile metals, with N_f increasing with decreasing σ_a (Figs. 1 and 2). Unfortunately S/N data for all materials tend to be marred by excessive scatter due to variations in factors such as surface condition or flaw distribution (Suresh, 1998), which can have a large effect on the crack initiation portion of the fatigue life. Additionally, from a perspective of identifying fatigue mechanisms, it is difficult to separate factors that govern the crack initiation and growth stages of the fatigue lifetime using total life S/N studies.

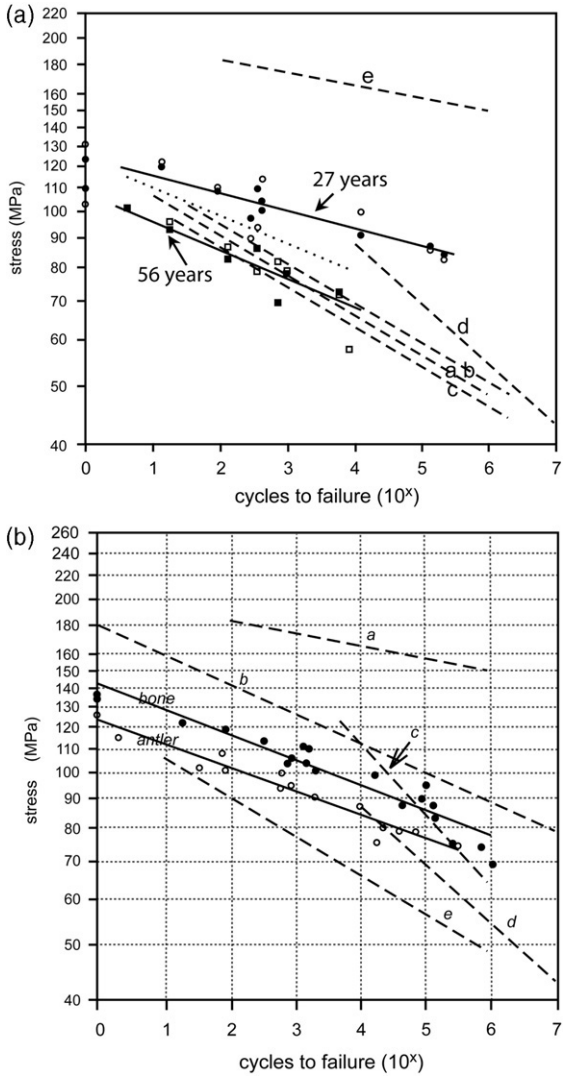

Fig. 2 – Fatigue stress-life S/N data for bone: (a) The effect of age in reducing the fatigue lifetimes is evident. Open symbols (circles and squares for 27 and 56 year old tissue, respectively) are the raw data, closed symbols are data normalized to account for modulus variations between samples within each age group, and the solid lines are regression fits to the solid symbols. The dotted line shows the 56 year old data normalized to account for the lower modulus relative to the 27 year old tissue. Dashed lines (marked a–e) show data from other studies, see Zioupos et al. (1996a) for more details. (b) The effect of species on fatigue lifetimes is shown. In addition to data for bovine femoral bone and red deer antler, dotted lines (marked a–e) show data from other studies: a, d, e— human, b, c— bovine (see Zioupos et al. (1996b) for details). Figures reproduced with permission from Zioupos et al. (1996a) and Zioupos et al. (1996b).

[1] Resulting S/N curves in certain materials, such as steels, can exhibit a plateau in the stress-life plot at ~10^6 cycles and beyond; this corresponds to a cyclic stress termed the fatigue or endurance *limit*, below which failure in principle does not occur (Suresh, 1998). In the absence of a fatigue limit, a fatigue or endurance *strength* is generally defined as the alternating stress to give a specific number of cycles to failure, typically 10^6 or 10^7 cycles (Suresh, 1998).

Due to this latter limitation in the understanding of fatigue mechanisms, results of such S/N fatigue studies will be only briefly reviewed before crack initiation and propagation are discussed separately.

3.1. *Fatigue life behavior of dentin*

The first published fatigue life study of bovine dentin was performed by Tonami and Takahashi (Tonami and Takahashi, 1997). They found that although the tensile strength was essentially identical for young (2–3 years old) and adult (3.5–6 years old) teeth, the 10^5-cycle tensile fatigue strength was significantly lower for the adult group. Microstructural differences between the two groups were mainly defined by a higher percentage of plugged or narrowed dentinal tubules in the adult group. Similar results were found for bending fatigue life tests involving both young and aged "transparent" human dentin, in the latter case the dentinal tubule lumens were largely filled with mineral (Kinney et al., 2005). For lives less than $\sim 10^5$ cycles the transparent dentin demonstrated significantly lower fatigue strength; however, the 10^6 cycle fatigue strengths were nearly identical. Another microstructural feature which can affect fatigue life is tubule orientation. Indeed, bend beams of human dentin with the tubules orientated parallel to the longitudinal beam axis demonstrated significantly lower fatigue lives than those with the tubules oriented parallel to the loading direction (Arola and Reprogel, 2006).

One mechanistic issue of concern when attempting to understand the fatigue behavior of dentin is whether the fatigue life is dependent on the number of cycles, the total time at load, or both. S/N fatigue studies on human dentin have shown that by changing the frequency from 20 to 2 Hz, the fatigue limit and fatigue lifetimes (in terms of cycles) were both lowered (Fig. 1), although when such S/N data were plotted on the basis of time, this frequency effect was reduced (Nalla et al., 2003a, 2004a). One might conclude from this that the mechanisms of fatigue-related failures in dentin may be predominantly time-, rather than cycle-, dependent, *i.e.*, there may not be a true cyclic fatigue mechanism. However, further experiments clearly revealed that the process of crack initiation was far easier under cyclic, as compared to static loads, and since S/N experiments include both the crack initiation and crack growth stages, which may have different time and cycle dependencies, the effect on each cannot be easily separated and the results cannot be simply interpreted. Accordingly, this topic will be revisited in Section 5.1 on crack propagation. Finally, one of those same studies also examined the effect of mean stress, and showed that dentin demonstrates metal-like behavior, with the fatigue life decreasing (at a given stress amplitude) with (i) increasing tensile mean stress, $\sigma_m = (\sigma_{max} + \sigma_{min})/2$, and (ii) increasing stress ratio, $R = \sigma_{min}/\sigma_{max}$ (Nalla et al., 2004a).

3.2. *Fatigue life behavior of cortical bone*

The fatigue life approach has been widely used for studies on cortical bone to investigate a variety of variables, including age (Zioupos et al., 1996a), donor species (Zioupos et al., 1996b), cyclic frequency (Lafferty and Raju, 1979; Caler and Carter, 1989; Currey, 1998; Zioupos et al., 2001), testing geometry (Zioupos et al., 1996a; Currey, 1998), and loading mode (Vashishth et al., 2001; Taylor et al., 2003). The effect of aging on the fatigue behavior has been addressed by Zioupos et al. (Zioupos et al., 1996a) who reported higher fatigue lifetimes for femoral bone taken from a 27-year old as compared to a 56-year old donor (Fig. 2(a)). The same authors also showed that bovine femoral bone is stronger in tensile fatigue than red deer antler (Fig. 2(b)) (Zioupos et al., 1996b). Data for bovine and human bone from a number of other studies are also included in Fig. 2. Although confounding factors such as differences in test frequency, loading mode, and temperature make direct comparisons difficult, data from Swanson et al. (Swanson et al., 1971) for human bone and from Carter and Caler (Carter and Caler, 1983) for bovine bone suggest that human bone is weaker than bovine bone in fatigue. However, it has recently been suggested that such differences may be age-related — most data for human bone, for obvious reasons, is from aged donors, and as such would be expected to have poorer mechanical properties (Taylor, 2003). Finally, Carter et al. have correlated microstructural differences to changes in the fatigue life. While higher density bone was shown to have longer fatigue lives (Carter and Hayes, 1976), an observed loss of fatigue strength with increased Haversian remodeling was larger than would be predicted by the density loss alone (Carter et al., 1976). Thus, while remodeling can be a positive factor in repairing fatigue damage, such results suggest that the susceptibility to future fatigue failure increases with increased remodeling.

With regard to test conditions, there is a definite effect of frequency on the S/N behavior, with higher frequencies giving higher fatigue-cycle lifetimes (Lafferty and Raju, 1979; Caler and Carter, 1989; Zioupos et al., 2001), this effect will be revisited in Section 5.2 in the context of fatigue crack growth mechanisms. Loading mode and test geometry have also been reported to have an effect on fatigue lifetimes in bone. For example, zero-compression loading generally gives only slightly higher lifetimes (10%–15%) than zero-tension loading (Caler and Carter, 1989). Vashishth et al. (Vashishth et al., 2001) reported a reduction in fatigue lifetimes when torsional loading was superimposed on tension–compression axial loading; similar results were seen for torsion as compared to compressive axial loading (Taylor et al., 2003). Data from Zioupos et al. (Zioupos et al., 1996a) suggests that fatigue lifetimes in human bone are progressively decreased by testing in (four-point) bending, rotating cantilever, and zero-tension loading. These latter results presumably reflect that fatigue damage will accumulate more readily in test geometries with larger statistical "sampling" volumes. These reported results of the fatigue of bone are, on the whole, in line with the typical fatigue behavior displayed by common engineering materials (Suresh, 1998), although variables such as temperature, donor age, etc., complicate comparisons between studies.

4. Damage accumulation and crack initiation

4.1. *Crack formation in teeth*

The first researchers to study the fatigue behavior of teeth examined the role of thermal cycling, and the induced cyclic

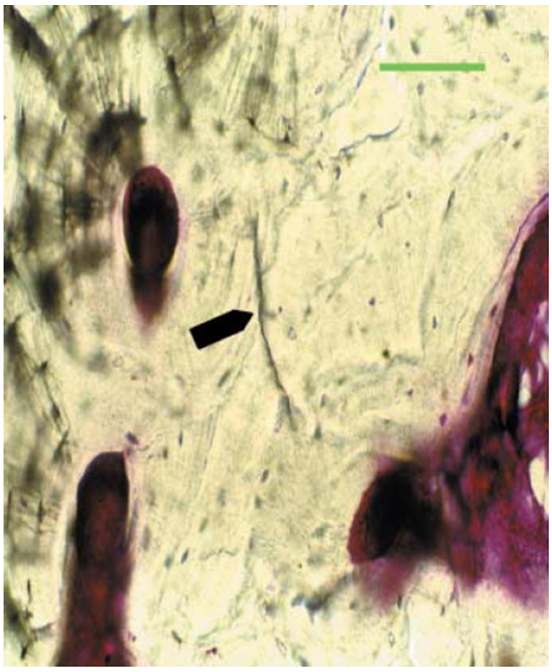

Fig. 3 – Fuchsin-stained microcrack in cortical bone. Scale bar = 50 μm. Figure reproduced with permission from Lee et al. (2003).

stresses, in causing damage accumulation in whole teeth (Brown et al., 1972). They concluded that thermal stresses due to cycling from 90 to 140 °F could cause cracking in both human and bovine teeth *ex vivo*, with cracks originating at the dentin–enamel junction and growing outward. This process occurred rapidly, and they concluded that cracks should be present in the enamel of most human teeth. The ease of crack formation in the enamel implies that crack growth in dentin should be the most important phase in determining the fatigue life of a whole tooth; accordingly, the fatigue crack growth properties of dentin have received considerably more attention in the literature, as will be discussed in Section 5.1.

4.2. *Microcrack formation and damage accumulation in cortical bone*

In contrast to teeth, microcrack formation and damage accumulation in cortical bone has been a lively area of research. This is because, in addition to being the precursor to the growth of a dominant fatigue crack to failure (*i.e.*, a stress fracture), microcracking damage is also believed to (i) adversely affect the acute (*i.e.*, prior to remodeling) mechanical properties of bone, (ii) trigger an *in vivo* remodeling and adaptation response of bone, and (iii) induce long term mechanical property changes in bone due to changes in microstructure from remodeling. Each of these items is addressed in this section.

Microdamage formation in bone was first systematically studied by Frost (Frost, 1960) using transmission light microscopy coupled with basic fuchsin staining as a way to differentiate between *in vivo* formed microcracks and damage from *ex vivo* sample preparation. Fig. 3 shows a typical fuchsin stained micrograph from Lee et al. (2003). This has been the dominant technique over the years for detecting microdamage in bone, *e.g.*, Burr et al. (1985), Burr and Stafford (1990), Norman and Wang (1997); however, in recent years variants on this technique have given improvements through the use of epifluorescence microscopy to allow easier crack identification (Lee et al., 1998), sequential labeling with various chelating agents to monitor crack propagation (Lee et al., 2000; O'Brien et al., 2002), and serial sectioning to determine three-dimensional crack shapes (O'Brien et al., 2000; Mohsin et al., 2006).

Studies to determine the 3-D shape of microcracks induced by bending loads have generally found that they form with an elliptical shape, with preferential growth occurring along the longitudinal axis of the bone (O'Brien et al., 2000; Mohsin et al., 2006). This is not surprising considering the anisotropy of the bone microstructure; indeed, the longitudinal direction has long been known to be the easiest direction for fracture under monotonic loading (Behiri and Bonfield, 1989; Nalla et al., 2003b). Thus, the ease of cracking in this direction appears to be ubiquitous in fracture and fatigue. While the secondary osteons act as a barrier for transverse cracking in bones, the cement lines which bind them appear to provide a weak path for crack propagation in both fatigue and monotonic loading conditions. Further discussion of crack propagation will follow in Section 5.2.

Several studies have been conducted to determine the microstructural sites where cracks initiate in human bone in response to fatigue cycling. Studies examining cross sections of human femur and tibia demonstrated that the majority of microcracks formed *in vivo* from normal human activity were located in the interstitial bone extending to the cement lines (Schaffler et al., 1995; Norman and Wang, 1997). It was found that $\leq$11% of the cracks formed entirely within the cement lines, indicating that although those are weak spots that affect the microcrack shape, they are not the weakest with respect to crack initiation. These studies also showed a very low incidence of crack initiation within the osteons, consistent with the concept that osteons are relatively resistant to cracking. Finally, investigations into *ex vivo* fatigue crack initiation using mechanically loaded longitudinal sections of equine bone noted a propensity for microcracks to form at stress concentrators such as Haversian and Volkmann canals (Fleck and Eifler, 2003); however, even ignoring the species difference it is doubtful that such observations should be directly compared with results from *in vivo* loading conditions as studied in Schaffler et al. (1995) and Norman and Wang (1997).

Some of those same studies have also investigated the role of sex and aging on fatigue microcrack formation, finding higher microcrack densities in specimens from female donors and older bones (Fig. 4) (Schaffler et al., 1995; Norman and Wang, 1997). Shaffler et al. investigated a large age range and reported little microcrack formation in specimens from donors younger than 40, and the microcracked regions that did form displayed numerous but small microcracks in more diffuse damage regions. In contrast, the microdamage that formed in older bones consisted of more sharply defined microcracks.

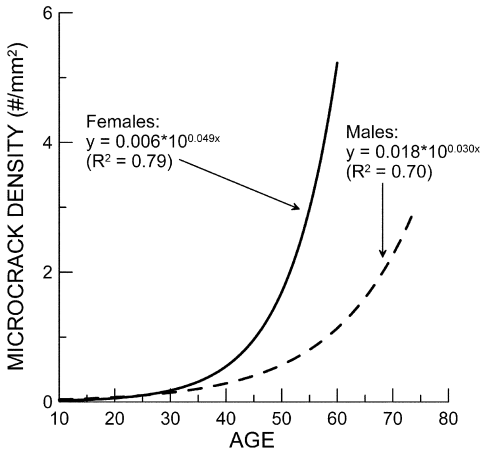

Fig. 4 – Plot of microcrack density versus age for human femoral cortical bone for both male and female donors based on data in Schaffler et al. (1995) due to *in vivo* loading. Note the increase in crack density with increasing age, and for female versus male donors.

Despite the extensive research on microcrack initiation in bone, very little is known about the actual mechanism of crack initiation. The most common tool for observation, optical microscopy, does not provide adequate resolution while electron microscopy of bone traditionally has had problems with either (i) dehydrating the sample during high resolution work or (ii) getting high enough resolution and/or hydration levels in environmental chambers. However, recent advances in environmental scanning and transmission electron microscopes will likely aid this area of research in the near future.

The degradation in mechanical properties as the result of fatigue microdamage accumulation has also been examined by various researchers. Carter and Hayes noted that damage in bovine bone from both rotating bend and zero-tension fatigue cycling causes a progressive loss in strength (Fig. 5) and stiffness during the fatigue life (Carter and Hayes, 1977a). The correlation of stiffness loss with fatigue damage accumulation has been subsequently observed by many researchers and in some studies has even been employed as a means to assess the amount of microdamage during fatigue tests (Pattin et al., 1996; Zioupos et al., 1996a,b; Danova et al., 2003; Fleck and Eifler, 2003). In addition to degraded strength and stiffness, it has also been found that fatigue induced microdamage decreases the fracture toughness of cortical bone (Yeni and Fyhrie, 2002).

With regard to bone remodeling, it has long been suspected that microdamage stimulates a remodeling response in cortical bone (Baker et al., 1972; Chamay and Tschantz, 1972; Carter and Hayes, 1977b; Martin and Burr, 1982), and both understanding and modeling this phenomena has been a continuing area of research over the years (Burr et al., 1985; Burr and Martin, 1993; Mori and Burr, 1993; Prendergast and Taylor, 1994; Bentolila et al., 1998; Martin, 2000; Lee et al., 2002; Martin, 2002; Waldorff et al., 2007). There is considerable experimental data supporting the idea that remodeling is targeted at regions where fatigue microdamage occurs (Burr et al., 1985; Burr and Martin, 1993; Mori and Burr, 1993; Bentolila et al., 1998). Furthermore, there is increasing evidence that osteocyte apoptosis is involved in regulating bone remodeling in response to microdamage (Verborgt et al., 2000, 2002). However, it is unclear if there is a single mechanism that governs all remodeling, particularly when one considers that not all bone remodeling appears to be targeted at repairing microdamage (Burr, 2002). Experiments on dog radii have lead to the hypothesis that only about 30% of bone remodeling is targeted at repairing microdamage (Burr, 2002). Furthermore, a recent *in vivo* study on rat bones indicates that the ability to remove microdamage by remodeling is diminished with age (Waldorff et al., 2007), which may suggest that targeted remodeling is also affected by aging. Thus, the question remains whether there are two separate types of remodeling, targeted and nontargeted, with different biological triggers that can be influenced separately or if there is a common set of triggers which causes remodeling in all cases (Martin, 2000; Burr, 2002; Martin, 2002).

Another result of bone remodeling is the induced change in microstructure, which can in turn affect the overall mechanical properties. As mentioned above, the cement lines between secondary osteons act as preferential cracking paths in both fracture and fatigue, while crack initiation appears to prefer interstitial bone to osteons or cement lines. Additionally, secondary osteons introduce new vascular channels which can increase the overall porosity of cortical bone with increasing osteon density. Thus, excessive remodeling due to fatigue microdamage can affect the balance of microstructural features, and in turn influence the mechanical properties. For example, it has been suggested that if bone remodeling levels are substantially higher than optimally needed to sustain bone quality, this may be a cause for bone fragility with aging (Heaney, 2003).

5. Fatigue crack propagation and mechanisms

To analyze fatigue crack propagation, a fracture mechanics methodology is best used where the crack-propagation rate, da/dN, is assessed in terms of the range in stress-intensity factor, ΔK,[2] defined as the difference between the stress intensity at the maximum and minimum of the loading cycle. Such results can often be simply fit to a Paris power-law formulation (Paris et al., 1961):

$$da/dN = C(\Delta K)^m, \quad (1)$$

where C and m (Paris exponent) are scaling constants. By using this approach it is possible to (i) isolate the specific mechanisms responsible for fatigue crack growth and (ii)

[2] The stress-intensity factor, K, is a global parameter which fully characterizes the local stress and deformation fields in the immediate vicinity of a crack tip in a linear-elastic solid, and thus can be used to correlate to the extent of crack advance. It is defined for a crack of length a as $K = Y\sigma_{app}(\pi a)^{1/2}$, where σ_{app} is the applied stress and Y is a geometry factor of order unity (Knott, 1976).

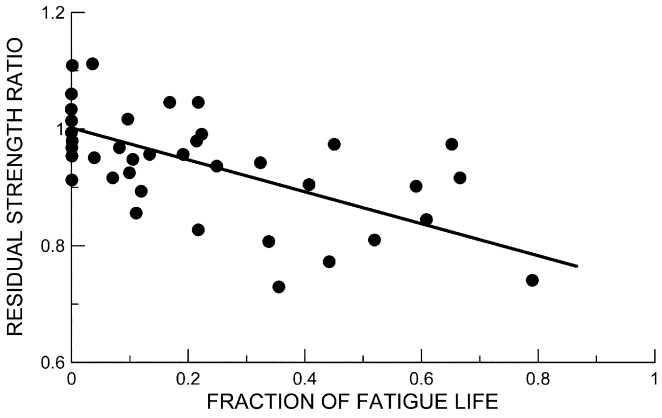

Fig. 5 – Plot of the residual strength ratio versus the fraction of the mean measured fatigue life showing the degradation in strength with fatigue cycling in bovine cortical bone. The residual strength ratio was determined by dividing the strength after fatigue cycling by the mean strength for specimens that had not been cycled. The fraction of the fatigue life was computed as the number of cycles applied to the specimen normalized by the mean fatigue life for samples tested to failure at that same cyclic stress level. The data have been replotted based on results in Carter and Hayes (1977a).

determine the microstructural or external factors which affect growth separately from crack initiation. This approach was first applied to cortical bone more than 30 years ago (Wright and Hayes, 1976); however, it received little subsequent attention until recently. Indeed, there has been considerable recent interest in understanding the fatigue crack growth behavior in both bone (Taylor, 1998; Akkus and Rimnac, 2001; Gibeling et al., 2001; Nalla et al., 2005a; Kruzic et al., 2006) and dentin (Arola et al., 2002; Arola and Rouland, 2003; Nalla et al., 2003a; Arola et al., 2005; Kruzic et al., 2005; Bajaj et al., 2006; Kruzic and Ritchie, 2006).

5.1. *Fatigue crack propagation in dentin*

Fatigue-crack growth behavior of dentin was first examined by Arola et al. (Arola et al., 2002; Arola and Rouland, 2003) for various orientations in bovine dentin. Those authors found that when the tubules were oriented in the same plane as fatigue-crack propagation, that growth was easier when the angle between the tubule axis and the growth direction was >45°, demonstrating the effect of the anisotropic dentin microstructure on the fatigue behavior. However, growth rates were not significantly affected when the tubule axis orientation was rotated out of the fracture plane. Interestingly, human dentin has demonstrated much lower fatigue strength when the tubules are oriented out of the cracking plane (Arola and Reprogel, 2006). This seeming contradiction can be explained by attributing this latter affect to differences in crack initiation and damage accumulation rather than differences in the crack growth properties. Such results illustrate the utility of studying crack initiation and propagation separately.

Those same researchers also demonstrated using bovine dentin that the fatigue crack propagation resistance decreases as the load ratio, $R = \sigma_{min}/\sigma_{max}$, is increased over the range of 0.1–0.5 (Arola et al., 2005). Such results are consistent with observations that the fatigue life of human dentin decreases with increasing load ratio (Nalla et al., 2004a). Neglecting differences in species, those studies together suggest that the decreased fatigue lives found by Nalla et al. are due to, at least in part, changes in the crack propagation resistance. The fact that dentin derives a portion of its fracture resistance from the extrinsic mechanism of crack bridging (Kruzic et al., 2003; Nalla et al., 2004b) gives a possible mechanism for this effect. At higher load ratios, bridges would be expected to fail quicker due the larger crack openings, while any associated crack closure effects would also be diminished, resulting in higher fatigue crack growth rates. Finally, in contrast to positive load ratios, a similar effect was not observed for negative (*i.e.*, tension–compression) load ratios; indeed, no significant differences were observed in the crack propagation behavior for samples tested with load ratios of 0.1, −0.25, and −0.5 (Arola et al., 2005).

Due to the small size of human teeth, crack propagation testing has been difficult using human dentin. The first fatigue crack growth results were reported by Nalla et al. (Nalla et al., 2003a) who used stiffness loss data to compute the fatigue crack growth rates for cantilever beam specimens. They reported a fatigue threshold, defined as the ΔK value where da/dN is roughly 10^{-10} m/cycle, of 1.06 MPa $\sqrt{m}$ and in general the results overlapped data on bovine dentin. More recent experiments have been performed using miniature compact tension specimens cut from human molars, with results showing considerable scatter in the fatigue crack growth behavior (Bajaj et al., 2006). Some of that scatter could be attributed to age, with older dentin (55 ± 14 yrs) exhibiting significantly higher power law exponents, m, and generally lower fatigue resistance than younger dentin (25 ± 7 yrs). Examination of the microstructure of the older dentin revealed most of the dentinal tubules to be filled with mineral (Bajaj et al., 2006), and the results were consistent with previous findings that older dentin has shorter S/N fatigue lives (Tonami and Takahashi, 1997; Kinney et al., 2005), suggesting the shorter lives were at least in part due to poorer fatigue crack growth resistance.

As mentioned in Section 3.1, one mechanistic question is whether fatigue crack growth in dentin is time-dependent,

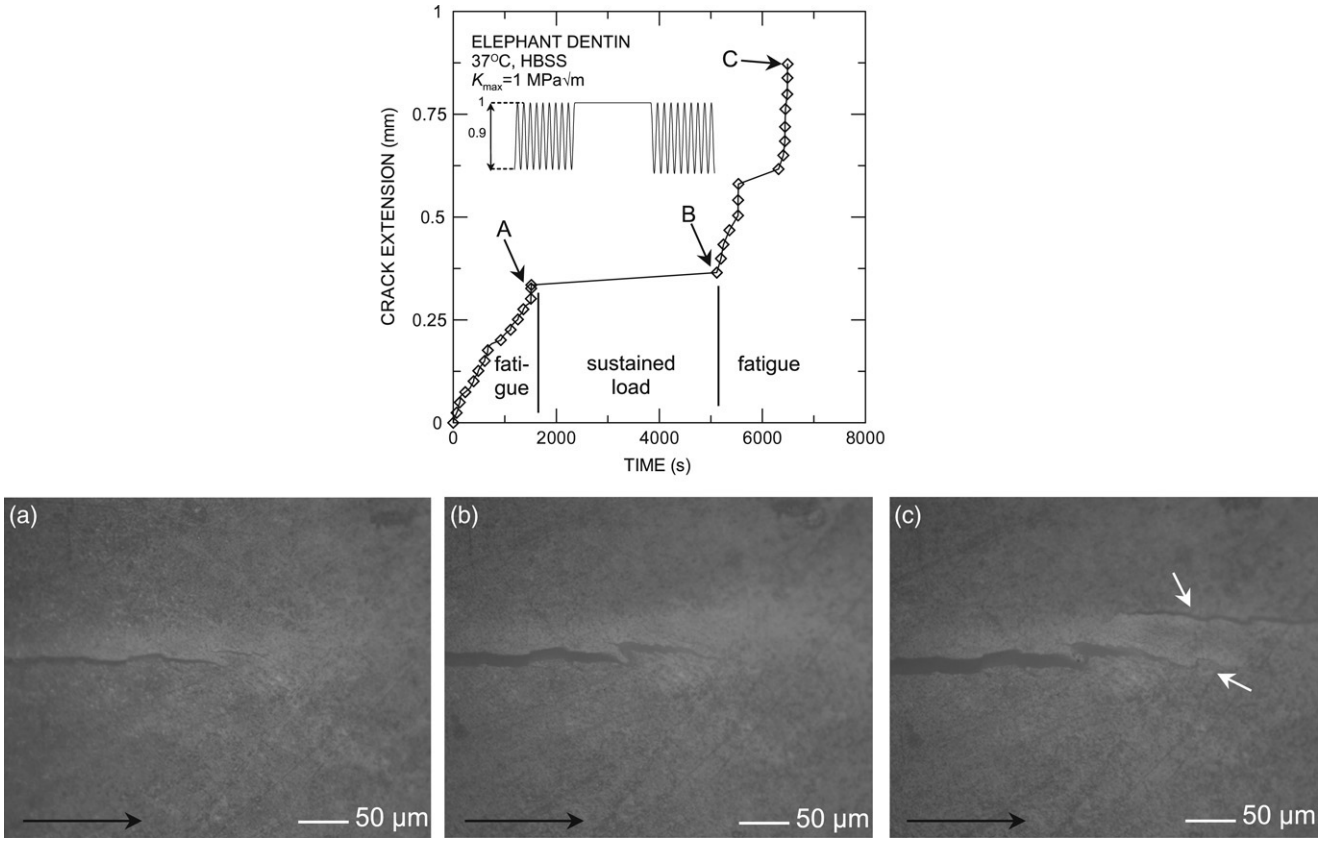

Fig. 6 – Results of "fatigue-sustained load-fatigue" tests in elephant dentin (in 37 °C HBSS) at a fixed K_{max} level of 1 MPa $\sqrt{m}$ (see inset), presented as plots of crack extension as a function of time, together with optical micrographs of the crack path at the end of each loading block. Note the substantial crack blunting during the sustained load block (b), and the subsequent crack extension during the second fatigue block (indicated by white arrows in (c)). The black arrow in each micrographs indicates the general direction of crack growth. Figure reproduced with permission from Kruzic et al. (2005).

cycle-dependent, or both. In order to answer that question a study was conducted using elephant dentin, which has similar microstructure to human dentin but allows much larger sample sizes (Kruzic et al., 2005). By using *in vitro* crack-growth experiments involving alternating time periods of cyclic and static loading, it was shown that cracks would essentially stop growing when the specimen was held at the maximum load of the cycle, only continuing when cyclic loading was resumed (Fig. 6). This indicates that the unloading portion of the fatigue cycle is essential for fatigue crack growth; accordingly, fatigue crack propagation in dentin was reasoned to be the result of a true cyclic fatigue mechanism, and not simply a succession of static fracture events integrated over the cyclic loading cycle (Kruzic et al., 2005). Additionally in that study, cyclic fatigue crack growth experiments were conducted over a range of cyclic frequencies (1–50 Hz) and a frequency dependence was observed for the crack growth rates, with higher growth rates associated with lower frequencies (Fig. 7). Based on the observed frequency dependence of fatigue-crack growth in dentin and direct observations of time-dependent crack blunting (Fig. 6), an alternating crack-tip blunting and re-sharpening mechanism (Fig. 8), similar to that observed in ductile metals, has been proposed as the primary cyclic fatigue crack growth mechanism in dentin (Kruzic et al., 2005). With this mechanism, for lower frequencies the longer time period near maximum load allows more crack blunting during each cycle, which in turn gives more crack growth per cycle and higher growth rates, as is observed.

5.2. *Fatigue crack propagation in cortical bone*

Fatigue crack propagation behavior in cortical bone was first studied using bovine bone by Wright and Hayes (Wright and Hayes, 1976). These authors found that the fatigue crack growth behavior of bone is similar to that seen in common engineering materials with da/dN increasing with increasing ΔK according to a power law (Eq. (1)), with values of m between 2.8 to 5.1 over growth rates of $da/dN \sim 7 \times 10^{-7}$ to $\sim 3 \times 10^{-4}$ m/cycle using cracks that were large compared to the microstructural features of the underlying material (Fig. 9). They also reported a measurable effect of frequency on the fatigue crack growth properties. More recently, a study by Gibeling *et al.* (Gibeling et al., 2001), measured $m \sim 10$ in osteonal equine bone (Fig. 9). For human bone, only one study has been reported to date; Nalla et al. (Nalla et al., 2005a) measured m values of ~4.4–9.5 for longitudinal fatigue-crack growth rates over a wide range from $\sim 2 \times 10^{-10}$ to

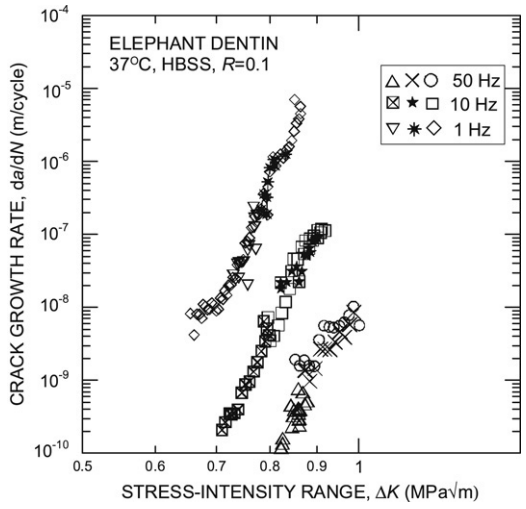

Fig. 7 – Fatigue data for elephant dentin (in 37 °C HBSS at $R = 0.1$) shown as a plot of the crack growth rates, da/dN, as a function of the stress-intensity range, ΔK, for frequencies of 1–50 Hz. Figure reproduced with permission from Kruzic et al. (2005).

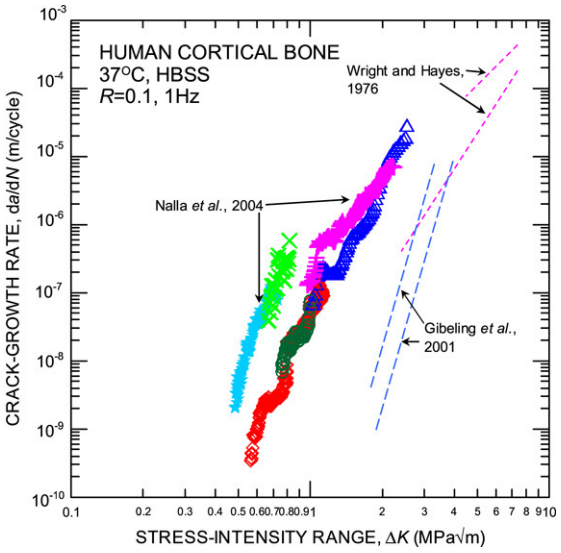

Fig. 9 – Variation in *in vitro* fatigue-crack growth rates, da/dN as a function of the stress-intensity range, ΔK, for bone in 37 °C HBSS ($R = 0.1$, 1 Hz frequency). Data shown as individual points are for human humeral cortical bone (Nalla et al., 2005a). Also included (as dashed lines) are data from Wright and Hayes (1976) for bovine bone and from Gibeling et al. (2001) for equine bone. Figure reproduced with permission from Ritchie et al. (2005).

$\sim 3 \times 10^{-5}$ m/cycle in human cortical bone taken from the humerus (Fig. 9).

As mentioned in Section 5.1, one mechanistic consideration is again whether fatigue crack growth is time-dependent, cycle-dependent, or both. Nalla et al. (Nalla et al., 2005a) demonstrated, using two different methods, a transition from predominantly time-dependent cracking at higher ΔK values to a true fatigue (cycle-dependent) mechanism at lower ΔK values, with this transition occurring at crack growth rates near 5×10^{-7} m/cycle. The first method involved experiments where cycling was periodically stopped, holding the specimen at a sustained load for a prescribed period of time before cycling again. The results indicated that at higher stress intensities the crack continued to propagate under sustained load, indicating a time-dependent mechanism (Fig. 10). Conversely, at lower stress intensities the crack arrested during the sustained loading intervals, indicating that cyclic loading was needed to propagate the crack. While a specific mechanism for subcritical crack growth under static loading has not been proposed, the cyclic mechanism in bone has been reasoned to involve crack extension via alternating blunting and re-sharpening of the crack tip (Nalla et al., 2005a), not unlike what is seen in many ductile materials, such as metals and polymers (Suresh, 1998). Fig. 8 shows a schematic of this proposed mechanism.

The fact that bone exhibits a regime of subcritical crack propagation that is time-dependent is not surprising. Early data on subcritical cracking under sustained quasi-static loading using bovine tibia and femur specimens showed higher driving forces (K or the strain energy release rate, G) were needed to grow cracks at higher velocities over the range of $\sim 10^{-5}$–10^{-3} m/s (Bonfield et al., 1978; Behiri

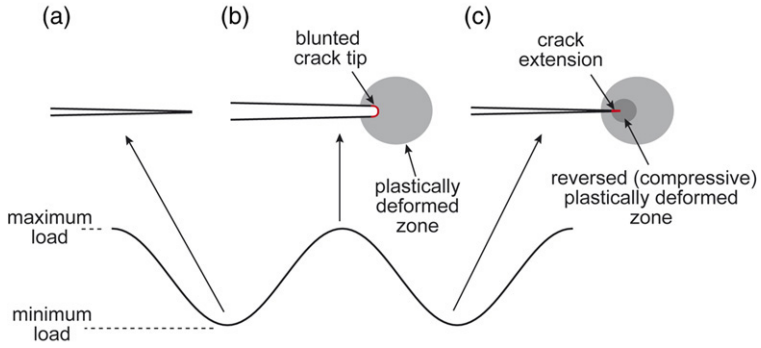

Fig. 8 – Schematic illustrating the proposed mechanism of "alternating, blunting and resharpening" for fatigue crack growth in dentin and bone. (a) shows the crack at the beginning of the loading cycle, (b) shows the blunted crack at the peak of the loading cycle, and (c) shows the resharpened, extended crack after unloading. Figure reproduced with permission from Kruzic et al. (2005).

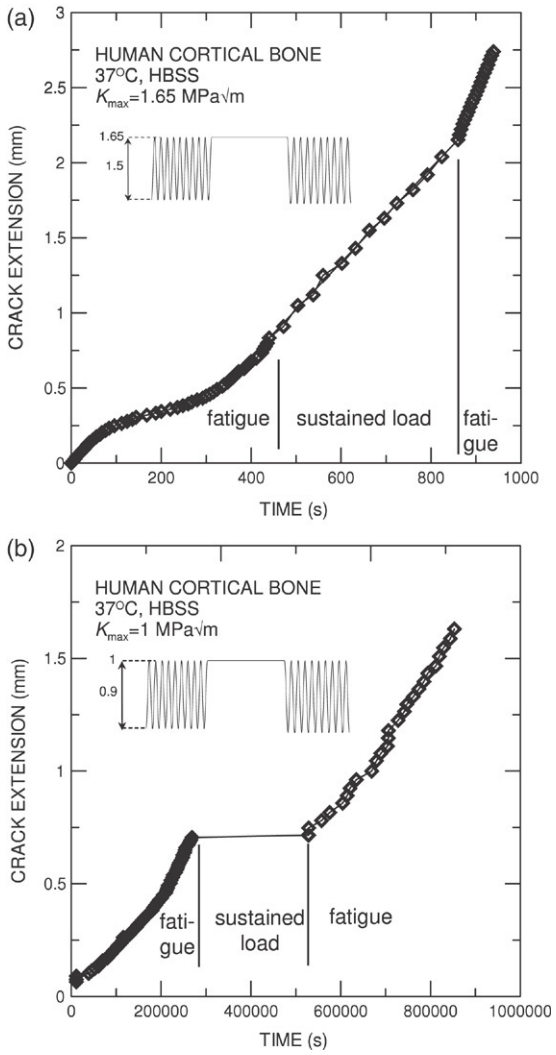

Fig. 10 – Results of "fatigue-sustained load-fatigue" tests at fixed K_{max} levels for human cortical bone (in 37 °C HBSS), presented as plots of crack extension as a function of time, for (a) K_{max} = 1.65 MPa √m and (b) K_{max} = 1 MPa √m. These results indicate that a time-dependent mechanism dominates at high stress intensities and growth rates, while a cycle-dependent mechanism dominates at lower values. Figure reproduced with permission from Nalla et al. (2005a).

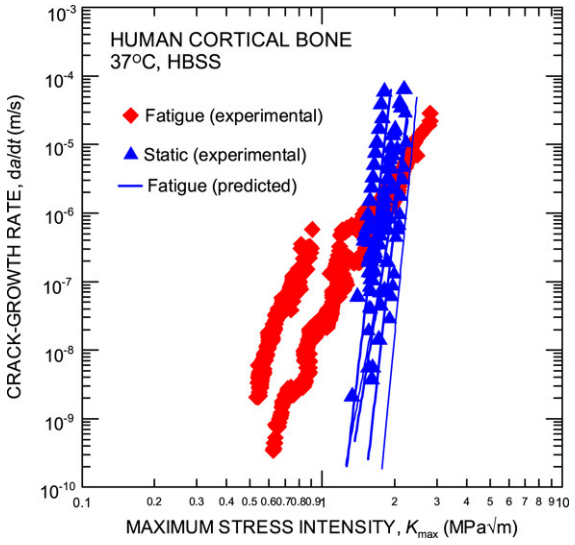

Fig. 11 – Comparison of the experimental *in vitro* crack growth rate results, expressed in terms of da/dt as a function of K_{max}, for human cortical bone under both cyclic and static loading (in 37 °C HBSS). Also shown are the predicted cyclic fatigue crack growth rates based on the sustained-load cracking data, using the Evans and Fuller approach (Evans and Fuller, 1974) (Eq. (2)). Note that experimentally measured growth rates in excess of the Evans–Fuller predictions, as shown for bone below ~5 x 10^{-7} m/cycle, implies the existence of a "true" cycle-dependent fatigue mechanism in this regime. Figure reproduced with permission from Nalla et al. (2005a).

and Bonfield, 1980, 1984). More recent studies (Nalla et al., 2005b), which have focused on slow crack growth in human humeri, reported similar results over a larger range of growth rates (~10^{-9}–10^{-4} m/s); higher stress intensities were again needed to grow cracks at higher growth rates (Fig. 11). Such behavior is analogous to that displayed by many engineering materials, such as ceramics and metals, which can exhibit time-dependent crack growth under sustained static loading (*e.g.*, Knott (1976), Lawn (1983)). In engineering materials, such behavior is typically associated with environmental effects, although it is unclear what role, if any, the physiological environment plays in subcritical cracking behavior in cortical bone.

The second method used to make the distinction between time and cyclic dependant growth involved the methodology devised by Evans and Fuller (Evans and Fuller, 1974), where the cyclic fatigue-crack growth rates are predicted solely from sustained-load cracking data over the full range of K_{max} values. The predictions are for materials that show *no true cyclic fatigue effects*, *i.e.*, on the premise that there is no effect on crack extension specific to cyclic loading and that fatigue-crack growth is merely the sum of the increments of sustained-load (static) cracking associated with the maximum load of each fatigue cycle. Using this approach and integrating (with respect to time) over the fatigue loading cycle, we obtain:

$$\frac{da}{dN} = A\int_0^{1/f}\left[\frac{1}{2}(K_{max}+K_{min}) + \frac{\Delta K}{2}(\sin(2\pi f t))\right]^n dt, \qquad (2)$$

where f is the cyclic test frequency, K_{max} and K_{min} are as previously defined, and A and n are the scaling constants as defined by the power-law relation used to fit the static-crack growth data shown in Fig. 11:

$$da/dt = AK^n. \qquad (3)$$

Thus, the predicted cyclic fatigue-crack growth rate behavior can be compared with that measured experimentally. If the predicted and experimental growth rates correspond well, the inference is that no true cyclic fatigue effect exists (for example, as seen in sapphire (Asoo et al., 2000)); however, if at a fixed stress-intensity range the experimentally measured

rates exceed the predicted rates, then this implies that cycle-dependent fatigue mechanisms are active. Such a comparison between experimentally measured fatigue-crack growth rates in human cortical bone with the Evans–Fuller predictions solely from sustained-load cracking data are shown in Fig. 11. At low crack-growth rates ($\sim 3 \times 10^{-10}$ to 5×10^{-7} m/cycle), the measured fatigue-crack growth rates (at a given K_{max}) clearly exceed the predicted rates, whereas at higher growth rates ($\sim 5 \times 10^{-7}$ to 1×10^{-5} m/cycle), the predicted rates are similar to slightly faster. This provides additional evidence that at low growth rates, a true cycle-dependent fatigue mechanism is operating in bone, whereas time-dependent sustained-load mechanisms appear to be more important at higher growth rates, the transition occurring between $\sim 10^{-7}$ and 10^{-6} m/cycle.

Another significant feature observed in cortical bone under static loading is that at growth rates below $\sim 10^{-9}$ m/s, significant crack blunting (crack-tip rounding) occurs which eventually leads to crack arrest (Nalla et al., 2005b). Thus, bone has a mechanism to arrest the growth of subcritical cracks driven by static (non-cyclic) loads where resharpening cannot occur during unloading.

Finally, extrinsic toughening is another factor which must be considered when assessing the fatigue behavior of cortical bone. Taylor first predicted that microcracks in bone should decelerate and accelerate during the early stages of propagation as they encounter microstructural barriers (Taylor, 1998). Experimental evidence for this behavior has been reported under both applied cyclic (Akkus and Rimnac, 2001; Kruzic et al., 2006) and static (Hazenberg et al., 2006) loads, with Kruzic et al. also reporting an overall increase in crack growth resistance with crack extension. Accordingly, an important factor which appears to influence the growth of microcracks in cortical bone is crack deflection due to cement lines, which in many cases act as microstructural barriers which cause microcracks to arrest (O'Brien et al., 2003, 2005). The overall increase in crack growth resistance has been associated with crack bridging (Kruzic et al., 2006). Bridges which form in the crack wake may sustain a portion of the load and reduce the local stress intensity range, ΔK, experienced at the crack tip, affecting the corresponding crack growth rates. This behavior leads to a crack size effect on the fatigue properties, *i.e.*, the crack propagation resistance increases as the bridging zone develops. Microstructural barriers such as cement lines may also be responsible for the formation of crack bridges as cracks imperfectly reconnect after deflecting around secondary osteons along the cement lines.

6. Fatigue life predictions

The fact that pre-existing microdamage is almost always present in teeth and bones makes the *damage-tolerant* approach an attractive method for assessing the fatigue life. This method is largely considered more accurate and conservative than the *S/N* approach because it does not consider the highly variable crack initiation portion of the lifetime, a reasonable assumption when pre-existing flaws are present. With this fracture mechanics based approach,

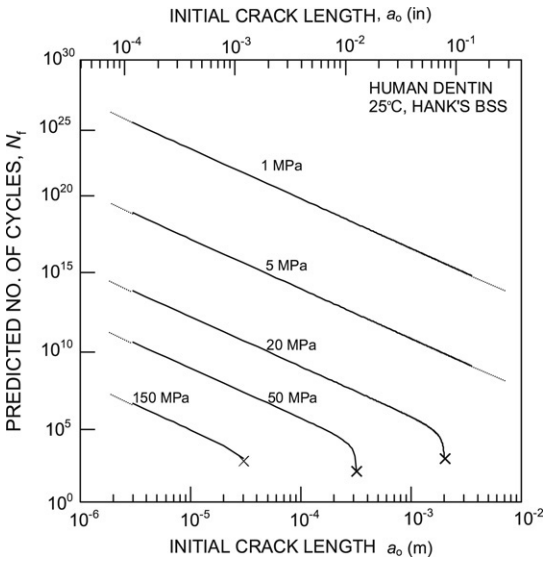

Fig. 12 – Predicted fatigue lives, based on a fracture-mechanics based damage tolerant life-prediction analysis, in terms of the number of loading cycles, N_f, and as a function of the initial flaw size, a_0, for human tooth dentin subjected to a range of in-service stresses. Figure reproduced with permission from Nalla et al. (2003a).

fatigue lives may be predicted by estimating the number of cycles required for an existing flaw to grow subcritically to a critical size, as defined by fracture toughness, using information relating da/dN to ΔK (Suresh, 1998). This is achieved by integrating the Paris crack-growth relationship in Eq. (1) between the limits of the initial flaw size, a_0, and the critical (final) flaw size, a_c, where the latter is computed based on the fracture toughness. The number of loading cycles to cause failure, N_f, is function of the in-service stress range, $\Delta\sigma$, and can be expressed (for $m \neq 2$) as:

$$N_f = \frac{2}{(m-2)CY^m(\Delta\sigma)^m\pi^{\frac{m}{2}}}[a_0^{(1-\frac{m}{2})} - a_c^{(1-\frac{m}{2})}] \quad (4)$$

where Y is a constant dependent upon the geometry, flaw size and shape. Complete details on this method may be found in Suresh (1998).

In dentin, which in general does not repair itself, this method should be quite accurate. Nalla et al. (Nalla et al., 2003a) carried out such predictions using data on human dentin, those results can be seen in Fig. 12 where the lifetimes are plotted as a function of the initial flaw size for several different applied (in-service) stresses. Finite element analyses of mandibular molars have indicated peak in-service stresses in dentin to be lower than in the enamel, and on the order of 10–43 MPa during mastication depending on the properties of the item being chewed (Dejak et al., 2003). A similar fatigue life analysis has been carried out for human cortical bone (Ritchie et al., 2005); however, in that case fatigue damage induced repair processes (see Section 4.2) allow for bone to function at loading levels/conditions where the predicted *in vitro* fatigue lifetimes are negligible. The fracture-mechanics lifetime prediction is instructive as it provides a worst-case estimate of the life of bone in the presence of subcritical

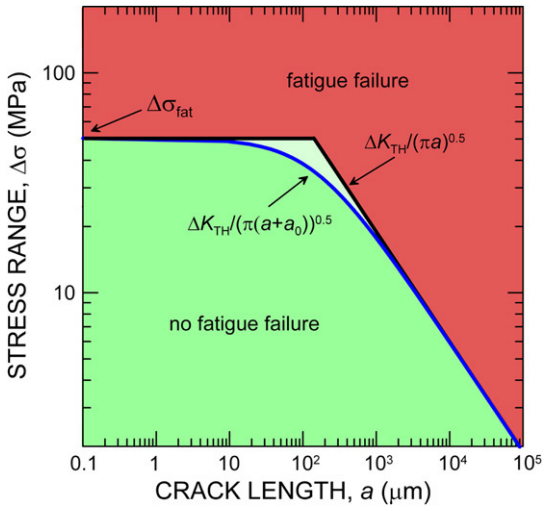

Fig. 13 – A Kitagawa–Takahashi diagram for human dentin which defines the stress range for fatigue failure (within ~10^6 cycles) as a function of crack size. The diagram is based on the limiting conditions for fatigue failure, which comprise the fatigue endurance strength ($\Delta\sigma_{fat}$) at small crack sizes, and the fatigue threshold stress-intensity range (ΔK_{TH}) at larger crack sizes. The transition between these limiting conditions is described by the traditional (Eq. (5)) and slightly modified El Haddad et al. approaches (El Haddad et al., 1979). This diagram defines a "failure envelope" of crack size/stress range combinations for fatigue failure in teeth. Figure reproduced with permission from Kruzic and Ritchie (2006).

cracking; however, a comprehensive prediction methodology needs to include repair processes as well. Accordingly, Taylor and Lee have made initial efforts to incorporate these equally critical aspects of the problem using computer simulations (Taylor and Lee, 2003).

One drawback of using the damage tolerant approach is that it is difficult to apply when crack sizes become small compared to the extent of local plasticity, or more importantly, the scale of the microstructure, *e.g.*, the size and spacing of the tubules in dentin (~micrometers) or osteons (~hundreds of micrometers) in cortical bone. As these crack sizes are not atypical in dentin and bone, it may be desirable to utilize a fatigue assessment method which marries the damage tolerant and *S*/*N* approaches and generates a description of how the limiting stress to cause fatigue failure varies with pre-existing crack size. The method of Kitagawa–Takahashi seeks to do exactly that, and it has been recently applied for human dentin as shown in Fig. 13 (Kruzic and Ritchie, 2006). The premise of the Kitagawa–Takahashi method is that the stress-intensity function can be plotted for the fatigue threshold, ΔK_{TH}, in terms of the stress range, $\Delta\sigma$, and the crack size, a, viz:

$$\Delta\sigma = \frac{\Delta K_{TH}}{Y\sqrt{\pi a}}. \quad (5)$$

Although the value of ΔK_{TH} is nominally independent of crack size, at small crack sizes this function tends to a limiting condition given by the fatigue endurance strength, which for dentin is $\Delta\sigma_{fat} \sim 50$ MPa. Accordingly, the Kitagawa–Takahashi diagram provides the "failure envelope" of crack size/stress range combinations where fatigue failure (in Fig. 13 within ~10^6 cycles[3]) may be a concern. The main strength of this approach is that it gives a straightforward and quantitative way to evaluate whether a known flaw will pose a failure risk under conditions of, for example, masticatory stresses in human teeth. Coupled with a non-destructive evaluation of flaw size, *e.g.*, from X-ray examination, this method may provide an instant quantitative assessment of the likelihood of premature tooth failure. Although traditional dental X-ray radiographs would be insufficient in resolution for such applications, state-of-the-art commercial X-ray computed tomography (CT) equipment developed recently for dental applications now achieves minimum resolutions of ~250 μm; accordingly, with slightly improved resolution there is hope that this approach could find significant clinical use.

7. Concluding remarks

Cortical bone and dentin are complex structural materials and a mechanistic understanding of how fatigue properties measured *in vitro* relate to the *in vivo* fracture risk associated with cyclic loading, as well as factors such as aging and disease, is still relatively limited. One goal is to determine the specific mechanisms involved in the fatigue and fracture of mineralized tissues, and to discover how these mechanisms relate to features within the respective microstructure. Such an understanding will greatly aid the development of treatments and/or prevention methods for conditions such as cracked tooth syndrome and stress fractures. As noted above, progress has been made with regard to a mechanistic understanding of cortical bone and dentin fatigue, but the degree of understanding is still not adequate. Consequently, we believe that the fatigue behavior of mineralized tissues will continue to remain an area of considerable research for the foreseeable future.

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[3] Since this approximates to roughly one year or so, for longer term predictions, *S*/*N* data out to ~10^7–10^8 cycles would be required.

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