

Mechanobiology of tooth movement

S. Henneman, J. W. Von den Hoff and J. C. Maltha

Department of Orthodontics and Oral Biology, Radboud University Nijmegen Medical Centre, The Netherlands

SUMMARY This review describes the mechanical and biological signalling pathways during orthodontic tooth movement and provides an update of the current literature. A theoretical model is introduced to elucidate the complex cascade of events after the application of an orthodontic force to a tooth. In this model, the events are divided into four stages: matrix strain and fluid flow, cell strain, cell activation and differentiation, and remodelling. Each stage is explained in detail and discussed using recent literature.

Introduction

Since the first extended reports at the end of the 19th century (Kingsley, 1880; Angle, 1900), there have been tremendous developments in the field of orthodontics. The acquired knowledge is being used to treat an increasing number of subjects with malocclusions that seek orthodontic solutions for their psychosocial, functional, or dental problems (Proffit, 2000).

A law in orthodontics is that a tooth can be moved through the alveolar bone when an appropriate orthodontic force is applied. This is based on the principle that a change in mechanical loading of a biological system results in strain, which subsequently leads to cellular responses aiming at adaptation of the system to the changed conditions. As a result of this principle, remodelling of the periodontal ligament (PDL) and the alveolar bone around a tooth takes place during orthodontic force application. It is possible to find detailed descriptions of processes occurring during orthodontic tooth movement in the literature (Krishnan and Davidovitch, 2006; Masella and Meister, 2006) but a concise overview of the induction processes is still lacking. Therefore, the aim of this review is to describe the mechanical and biological processes taking place during orthodontic tooth movement and to provide an update of the current literature. To elucidate the complex cascade of events after the application of an orthodontic force on a tooth, a new theoretical model based on the existing knowledge is introduced.

Terminology

In orthodontics, the two sides of a tooth during tooth movement are normally called the pressure and tension side. The term 'pressure' suggests a loading of the PDL and the bone by the orthodontic force. However, this is not what occurs. The apparent contradiction can be explained by two phenomena. First, the presence of collagen fibres of the PDL that connect the tooth with the alveolar bone. At the so-called pressure side, these fibres are unloaded leading to unloading of the alveolar bone, resulting in its resorption (Melsen, 2001). Second, a redistribution of fluid in the PDL

leads to a rapid return to normal tissue fluid pressure within the periodontal space. The above explains the importance of the correct use of terminology in orthodontics. To avoid further confusion, the more accurate terms resorption and apposition side instead of pressure and tension side will be used.

Theoretical model

The model shown in Figure 1 demonstrates the main processes taking place after the application of an orthodontic force. In this model, the force is assumed to be exerted on a single tooth leading to bodily tooth movement. A period of arrest in movement often takes place after application of a force, caused by local tissue necrosis (Rygh, 1973; Brudvik and Rygh, 1994). Tooth movement through the bone can only start after the removal of this necrotic or hyalinized tissue by phagocytic cells such as macrophages, foreign body giant cells, and possibly osteoclasts (Okumura, 1982; Nakamura *et al.*, 2001). Since it is not essential for the bone remodelling process during tooth movement and, for the sake of clarity, this hyalinization period and the subsequent inflammatory reaction is not included in the model. The attachment of the tooth to the bone is schematically shown in Figure 2. A visualization of the changes in the system that take place after external force application is also shown.

The theoretical model describes four stages in the induction of tooth movement. These stages are as follows: (1) Matrix strain and fluid flow (Figure 1a). Immediately after the application of an external force, strain in the matrix of the PDL and the alveolar bone results in fluid flow in both tissues. (2) Cell strain (Figure 1b). As a result of matrix strain and fluid flow, the cells are deformed. (3) Cell activation and differentiation (Figure 1c). In response to the deformation, fibroblasts and osteoblasts in the PDL as well as osteocytes in the bone are activated. (4) Remodelling (Figure 1d). A combination of PDL remodelling and the localized apposition and resorption of alveolar bone enables the tooth to move. These stages will be described in more detail in the following sections.

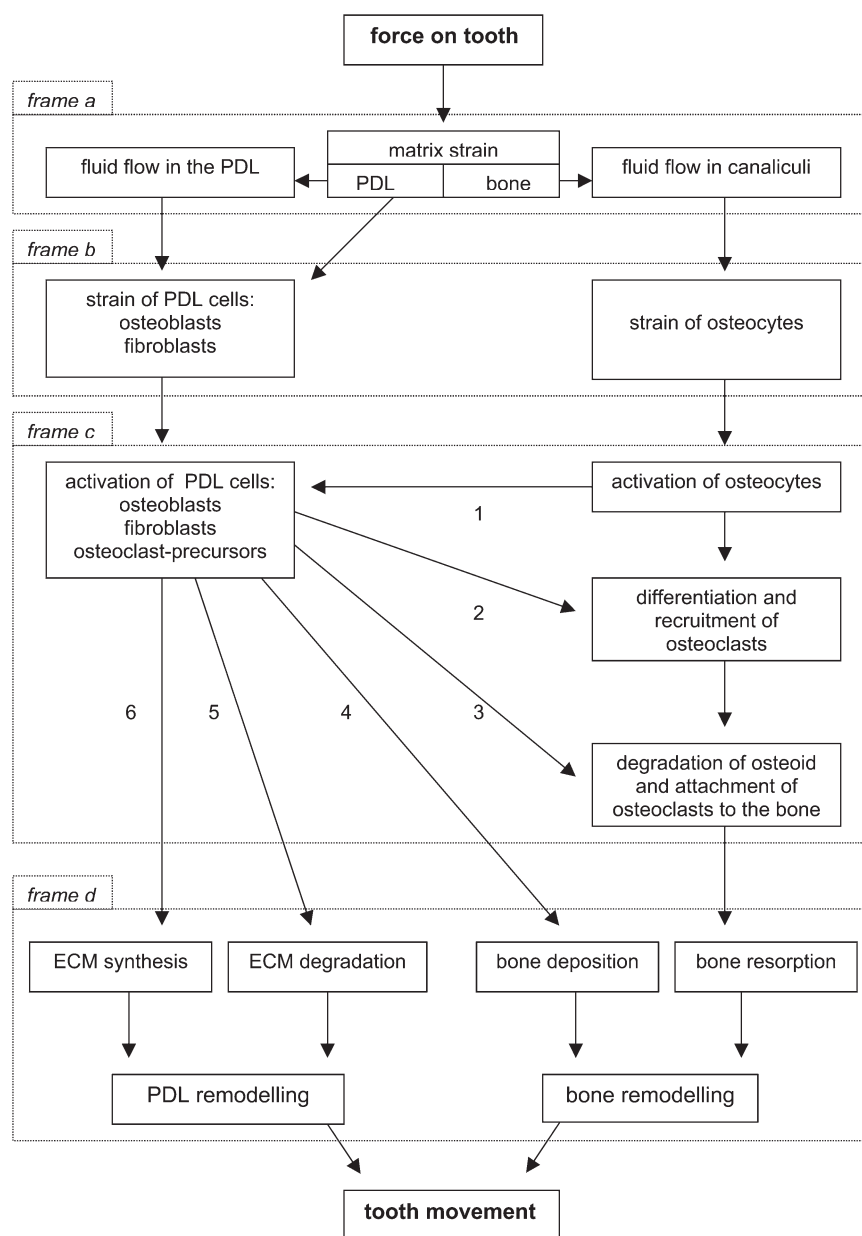


Figure 1 A theoretical model of tooth movement. The model describes four different stages in the induction of tooth movement. Frame (a) represents matrix strain and fluid flow, (b) cell strain, (c) cell activation and differentiation, and (d) remodelling of the periodontal ligament (PDL) and bone.

Matrix strain and fluid flow (Figure 1a)

Immediately after the application of a force, the tooth moves within its socket for a certain distance. The amount of movement depends on the biomechanical properties and the dimensions of the PDL. This movement leads to a positive strain (tensional deformation) within the PDL at the future apposition side of the root (Reitan, 1951) and, therefore, a stretching of the collagen fibres, which connect the tooth to the bone (Rygh *et al.*, 1986; Melsen, 1999). At the future resorption side of the root, a negative strain (compressive deformation) is induced within the PDL

(Reitan, 1951) and, consequently, the fibres are relaxed (Melsen, 1999; Binderman *et al.*, 2002). The strain depends on the material properties of the PDL and the applied force. The material properties of the PDL have been analysed by measuring tooth displacement in relation to an applied load in both animal and human experimental settings (Chiba and Komatsu, 1993; van Driel *et al.*, 2000; Yoshida *et al.*, 2001; Komatsu *et al.*, 2004; Cronau *et al.*, 2006). However, these studies have yielded highly variable results. The data have been used in finite element models in an attempt to calculate the strain distribution within the PDL under

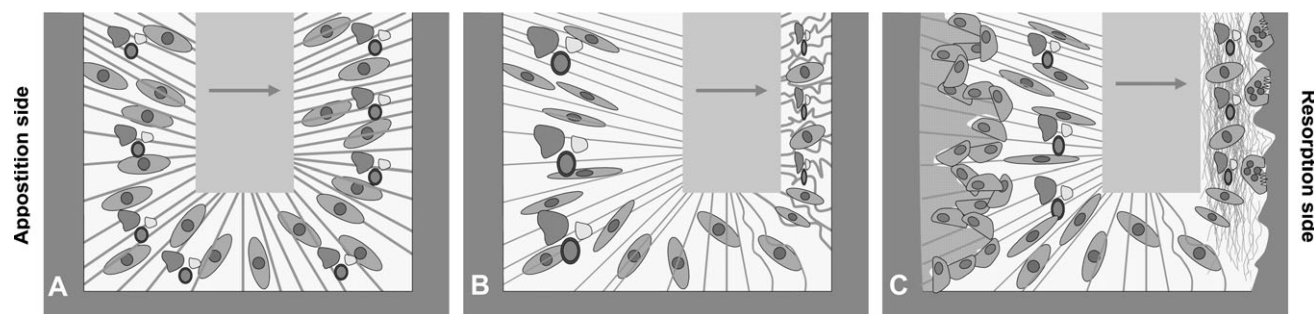


Figure 2 Schematic drawing of a tooth, the periodontal ligament with cells and alveolar bone. (a) An external force is applied (arrow). (b) At the apposition side, fibres are stretched. Compression of fibres takes place at the resorption side. (c) After prolonged force application, bone formation by osteoblasts can be found at the apposition side and osteoclasts resorb the bone at the resorption side.

specific loading conditions (van Driel *et al.*, 2000; Natali *et al.*, 2004; Cattaneo *et al.*, 2005). Increasing evidence exists for a non-linear and time-dependent relationship between force and displacement, indicating that the PDL is viscoelastic (Yoshida *et al.*, 2001; Cronau *et al.*, 2006). This behaviour can be described with the viscoelastic properties of only the PDL fibres (Sasano *et al.*, 1992; van Driel *et al.*, 2000; Komatsu *et al.*, 2004; Natali *et al.*, 2004), but a two-phase fibre-reinforced viscoelastic model seems to be more realistic. The latter model predicts an almost immediate fluid flow in the PDL after force application at both the apposition and resorption sides, followed by an increasing strain of the viscoelastic matrix, which is mainly determined by the collagen fibres. This model can very well explain *in vivo* data on the mechanical behaviour of the PDL (unpublished data).

In addition, the external force also results in a strain in the alveolar bone at the apposition side through the collagen fibre bundles that connect the tooth to the bone (Cronau *et al.*, 2006; Meikle, 2006). An important theory that describes the reaction of bone to strain involves the effect of fluid flow on bone cells (Weinbaum *et al.*, 1994; Cowin *et al.*, 1995; Mak *et al.*, 1997). This fluid shear stress theory is based on the presence of osteocytes entrapped in lacunae within the bone. These cells are interconnected by protrusions that run through tiny channels in the bone called canaliculi. The strain of the bone results in a fluid flow through the canaliculi leading to shear stress on the osteocytes, which are then activated. It has been suggested that in areas of reduced canalicular fluid flow, apoptosis of osteocytes occurs, which subsequently attracts osteoclasts to the site (Burger *et al.*, 2003; Tan *et al.*, 2006). This could be the case at the resorption side of the tooth where an unloading of the bone might result in a reduction of fluid flow. Indeed, it has been shown in mice that unloading of bone leads to increased osteocyte apoptosis followed by bone resorption (Aguirre *et al.*, 2006). This concept of mechanosensing of osteocytes by strain-derived canalicular fluid flow is supported by *in vitro* data (Klein-Nulend *et al.*, 1995c; Ajubi *et al.*, 1996;

Owan *et al.*, 1997; Westbroek *et al.*, 2000; Tan *et al.*, 2006). Studies in animal models also support this theory (Pitsillides *et al.*, 1995; Turner *et al.*, 1995) and the actual canalicular fluid flow itself has been shown in the rat tibia (Knothe Tate *et al.*, 2000).

Two alternatives for the fluid flow theory have been proposed. The first assumes a direct mechanical stimulus on cells within the bone by an external force (Kimmel, 1993; Mullender and Huiskes, 1995). This direct loading effect is supported by *in vitro* studies. However, the strains used were much higher than those believed to occur in bone (Harter *et al.*, 1995; Brand *et al.*, 2001). Direct mechanical loading with strain levels similar to those measured *in vivo* evokes no cellular reaction in human osteocytes *in vitro* (Owan *et al.*, 1997; You *et al.*, 2000).

The second alternative theory is based on the principle that bone microdamage evokes a cellular response (Mori and Burr, 1993; Taylor and Lee, 2003). This microdamage theory developed from the hypothesis that microcracks occur in the bone as a result of material fatigue. This might lead to apoptosis of osteocytes around the cracks which, as mentioned previously, attracts osteoclasts to the site (Noble *et al.*, 1997; Noble 2005). Animal studies show increased amounts of apoptotic osteocytes in combination with increased numbers of osteoclasts after mechanical loading of bone (Noble *et al.*, 2003; Clark *et al.*, 2005). Furthermore, increased numbers of microcracks have been found at the resorption side during the initial phase of orthodontic tooth movement in pigs (Verna *et al.*, 2004). This suggests that not only reduced fluid flow but also microcracks might cause apoptosis of osteocytes. The microcracks reflect the initial damage of the bone that is subsequently remodelled.

In summary, the application of an external force to a tooth strains the matrix of the PDL and evokes a fluid flow in the tissue. Simultaneously, according to the fluid flow theory, a strain in the bone induces canalicular fluid flow, which results in a shear stress on osteocytes. In addition, microdamage of the bone after force application might be involved.

Cell strain (Figure 1b)

Direct deformation of PDL cells is possible via transduction of strain through cell-matrix attachments (Beertsen *et al.*, 1997) and indirect deformation might be induced by fluid flow (Davidovitch, 1991). The cell-matrix attachments are formed by binding of the extracellular domains of integrins to extracellular matrix (ECM) proteins. Integrins are transmembrane proteins with an extra- and intracellular domain. Inside the cell, the cytoplasmic domains of the integrins connect to the cytoskeleton via a multiprotein complex (Goldmann, 2002). This focal adhesion complex not only transduces matrix strain to the cytoskeleton but also activates protein kinases that initiate a variety of intracellular signalling pathways (Hynes, 1992; Wang and Thampatty, 2006). It is not exactly clear how signal transduction after indirect deformation by fluid flow takes place, although the cytoskeleton is probably also involved. Alternatively, specific flow receptors on the cell surface have been proposed (Cherian *et al.*, 2005; Wall and Baner, 2005).

Whatever the exact mechanism, PDL cells need to be highly sensitive to mechanical stimuli. This is indeed shown by *in vitro* studies, in which PDL fibroblasts react to direct deformation by the production of cytokines and other mediators, and matrix metalloproteinases (MMPs) that degrade collagen (Von den Hoff, 2003; Yamaguchi *et al.*, 2004; Snoek-van Beurden and Von den Hoff, 2005). Some important mediators will be discussed in the next section.

Many *in vitro* studies have employed culture dishes with a flexible bottom that is stretched, which directly deforms the cells (Baner *et al.*, 1985). Indirect mechanical deformation has been performed *in vitro* by the application of a pulsating fluid flow. These data show that not only direct cell deformation but also fluid flow-induced deformation leads to cellular responses in PDL fibroblasts (van der Pauw *et al.*, 2000). *In vivo*, mechanical stimulation by orthodontic forces also increased the levels of mediators in the PDL such as interleukins (Davidovitch *et al.*, 1988; Alhashimi *et al.*, 2001). Besides fibroblasts, osteoblasts within the PDL are also sensitive to mechanical stimulation. Mechanosensing of osteoblasts was shown by the release of signalling molecules such as prostaglandins by human osteoblasts after direct and indirect deformation (Bakker *et al.*, 2003; Mullender *et al.*, 2004; Tang *et al.*, 2006).

It was assumed that a shear stress on osteocytes occurs within the bone as a result of canalicular fluid flow during orthodontic force application. Similar to the activation of PDL cells by fluid flow, the signal might be transduced to the osteocytes through specific receptors or through deformation of the cytoskeleton (Duncan and Turner, 1995). Osteocytes respond to fluid flow *in vitro* by the production of mediators such as nitric oxide (NO) and prostaglandins (Klein-Nulend *et al.*, 1995b; Westbroek *et al.*, 2000).

In summary, after force application both matrix strain and fluid flow in the PDL and the bone cause deformation of

cells. Through integrin signalling and other transduction pathways, mediators are produced that activate several types of cells.

Cell activation and differentiation (Figure 1c)

As mentioned, the production of mediators by PDL and bone cells during mechanical stimulation indicates that these cells become activated. In frame *c*, the arrows indicate which cellular processes are induced by the mediators. Arrow 1 indicates the effect that activated osteocytes have on cells in the PDL. Precursors in the PDL are stimulated to differentiate into osteoblasts through factors produced by activated osteocytes (Dereka *et al.*, 2006). Examples of these factors are bone morphogenic proteins (2, 6, and 9) and platelet-derived growth factor that also stimulate osteoblast activity (Cheng *et al.*, 2003; Singhatanadgit *et al.*, 2006). Osteocytes also respond to strain *in vitro* by the production of cytokines, NO, prostaglandins, and tumour necrosis factor- α (Klein-Nulend *et al.*, 1995b,a; Ajubi *et al.*, 1996; Westbroek *et al.*, 2000; Kurata *et al.*, 2006). These *in vitro* studies support the theory that certain cytokines produced by osteocytes activate osteoclast precursors in the PDL at the resorption side, while NO inhibits the activity of osteoclasts at the apposition side in rats (Yoo *et al.*, 2004).

The activation of osteoclast precursors and the differentiation into osteoclasts by factors produced by PDL cells are represented by arrow 2. At the resorption side, soluble factors such as colony-stimulating factor, receptor activator of nuclear factor kappa β ligand (RANKL), osteoprotegerin, and bone morphogenic proteins regulate osteoclast differentiation has been shown *in vitro* (Nomura and Takano-Yamamoto, 2000; Zhao *et al.*, 2002; Kurata *et al.*, 2006) and, *in vivo*, during orthodontic tooth movement in rats (Shiotani *et al.*, 2001). These factors are produced by osteocytes present in the alveolar bone and by osteoblasts and fibroblast present in the PDL (Oshiro *et al.*, 2002). Colony-stimulating factor is of importance during the first steps of differentiation. RANKL, and its receptor RANK, stimulate the further differentiation of osteoclasts. Osteoprotegerin is a decoy receptor for RANKL that prevents its binding to RANK and thereby further differentiation (Theoleyre *et al.*, 2004).

Before actual resorption of bone can take place, osteoblasts have to degrade the non-mineralized layer of the osteoid (arrow 3). Only after degradation of this layer through MMP activity, can the differentiated osteoclasts attach to the bone surface (Birkedal-Hansen *et al.*, 1993). This attachment is mediated by specific integrins ($\alpha v \beta 3$; Gay and Weber, 2000), and it is stimulated by osteopontin (OPN) produced by osteoblasts and osteocytes. During orthodontic tooth movement, increased levels of OPN have been found at the resorption side (Terai *et al.*, 1999).

Bone formation at the apposition side of the tooth is a combination of ECM synthesis and mineralization (arrow 4). *In vitro* studies show that loading of PDL cells results in

an increased production of alkaline phosphatase, osteocalcin, and other non-collagenous matrix proteins (Matsuda *et al.*, 1998; Ozaki *et al.*, 2005; Yang *et al.*, 2006). These factors might stimulate precursors in the PDL to differentiate into osteoblasts, leading to subsequent bone deposition. After mechanical stimulation *in vitro*, osteoblasts produce NO, which is, among others, a mediator of bone formation (Owan *et al.*, 1997; You *et al.*, 2000; Burger *et al.*, 2003; Mullender *et al.*, 2004).

The production of factors that regulate ECM degradation by PDL cells is represented by arrow 5. PDL fibroblasts and osteoblasts react to mechanical stress *in vitro* by the production of inflammatory mediators such as prostaglandins and enzymes such as MMPs and cathepsins that stimulate ECM degradation through autocrine and paracrine actions (Owan *et al.*, 1997; Howard *et al.*, 1998; You *et al.*, 2000; Yamaguchi *et al.*, 2004). *In vitro* studies have also shown that not only the unloading of PDL but also dermal fibroblasts leads to a reduction of collagen synthesis and an increased expression of ECM-degrading MMPs (Langholz *et al.*, 1995; Xu and Clark, 1996; Von den Hoff, 2003). It is clear that degradation of the ECM of periodontal tissues after orthodontic force application takes place both after loading and unloading of cells. This is also supported by the presence of increased MMP levels at both the resorption and apposition sides during orthodontic tooth movement (Apajalahti *et al.*, 2003; Takahashi *et al.*, 2003, 2006; Ingman *et al.*, 2005).

Besides the degradation of ECM, new ECM is also synthesized during remodelling of the periodontal structures around the tooth (arrow 6). Increased levels of collagen synthesis were found at both the resorption and apposition sides after orthodontic force application in humans (Bumann *et al.*, 1997). Several mediators produced by activated PDL and bone cells stimulate ECM synthesis and reduce its degradation. Examples are members of the transforming growth factor- β (TGF- β) superfamily (Nahm *et al.*, 2004). Increased levels of transforming growth factor- β , cathepsins B and L, and interleukin-1 beta were also found in the crevicular fluid of orthodontically moved teeth in humans and at the apposition side of rat teeth after orthodontic force application (Uematsu *et al.*, 1996a,b; Wang *et al.*, 2000; Iwasaki *et al.*, 2001; Yamaguchi *et al.*, 2004). In addition, ECM breakdown is also inhibited by the tissue inhibitors of MMPs produced by PDL cells (Nahm *et al.*, 2004; Verstaappen and Von den Hoff, 2006).

In summary, fibroblasts, osteoblasts, osteocytes, and osteoclasts are part of a complex regulatory network that induces PDL and bone remodelling during orthodontic tooth movement.

Remodelling (Figure 1d)

Under physiological conditions, the synthesis and degradation of the periodontal structures is at a low level to maintain tissue homeostasis (Figure 2a). After the application

of an external force, this balance is disturbed and increased remodelling of both PDL and bone leads to tooth movement (Figure 2b,c). At the resorption side, PDL tissue and alveolar bone is degraded to create space for the moving tooth while new PDL tissue is simultaneously formed to maintain the attachment. The extensive remodelling of the PDL matrix takes place after the activation of fibroblasts in the PDL. Meanwhile, osteoclast precursors migrate to the bone surface and differentiate into osteoclasts. After differentiation, the activated osteoclasts attach to the bone surface by means of specific integrins (Gay and Weber, 2000). The attached osteoclasts undergo morphological changes and develop specific functional characteristics. The clear zone seals off the bone surface from its environment, the body of the osteoclast contains an extensive lysosomal system, and the ruffled border is the site where the actual resorption takes place (Hill, 1998). The osteoclast releases hydrogen ions at the ruffled border, which dissolve the anorganic matrix and, after the organic matrix is resorbed by enzymes such as cathepsins and MMPs (Teitelbaum *et al.*, 1997; Phan *et al.*, 2004), the attachment of the principal fibres of the PDL to the bone is lost. The non-functional fibres that mainly contain type I collagen are degraded and replaced by a loose connective tissue mainly containing type III collagen (Pilon, 1996).

At the apposition side, the principal fibres are stretched and remodelling of the PDL takes place. New bone is formed by the activated osteoblasts that first produce new ECM and then mineralize this in a unidirectional manner. At a later stage, when the new layer of bone becomes thicker, some osteoblasts will become entrapped in the bone and turn into osteocytes. The principal fibres of the PDL will also be entrapped in the newly formed bone as Sharpey's fibres. In the meantime, new PDL matrix is formed to maintain the width of the PDL and the attachment of the tooth to the alveolar bone. This new PDL contains thick principal fibres of mainly type I collagen for correct attachment of the tooth to the bone. Both the resorption and apposition sides show upregulation of collagen synthesis after orthodontic force application (Bumann *et al.*, 1997) but the type of collagen is different. A much higher increase of collagen type I was found at the apposition side compared with the resorption side after orthodontic force application in rats (Nakagawa *et al.*, 1994).

Conclusion

The introduced theoretical model (Figure 1) is a schematic overview of the processes taking place after the application of an orthodontic force. The strain in the matrix of the PDL and the alveolar bone immediately after force application, resulting in a fluid flow in both tissues is represented by (a). As a result of matrix strain and fluid flow, cells are deformed (b). In response to the deformation, fibroblasts and osteoblasts in the PDL as well as osteocytes in the bone are activated (c).

In *d*, a combination of PDL remodelling, and the localized apposition and resorption of alveolar bone enables the tooth to move. This model might offer the clinician a better insight into the processes taking place during orthodontic tooth movement and a greater understanding of the biological consequences of orthodontic treatment.

Address for correspondence

J. W. Von den Hoff
Department of Orthodontics and Oral Biology
Radboud University Nijmegen Medical Centre
309 Tandheelkunde
Postbus 9101
6500 HB Nijmegen
The Netherlands
E-mail: h.vondenhoff@dent.umcn.nl

References

- Aguirre J I 2006 Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *Journal of Bone and Mineral Research* 21: 605–615
- Ajubi N E, Klein-Nulend J, Nijweide P J, Vrijheid-Lammers T, Alblas M J, Burger E H 1996 Pulsating fluid flow increases prostaglandin production by cultured chicken osteocytes—a cytoskeleton-dependent process. *Biochemical and Biophysical Research Communications* 225: 62–68
- Alhashimi N, Frithiof L, Brudvik P, Bakht M 2001 Orthodontic tooth movement and *de novo* synthesis of proinflammatory cytokines. *American Journal of Orthodontics and Dentofacial Orthopedics* 119: 307–312
- Angle E H 1900 Treatment of malocclusion of the teeth and fractures of the maxillae. Angle's system. 6th edn. S S White Dental Manufacturing Co., Philadelphia
- Apajalahti S, Sorsa T, Railavo S, Ingman T 2003 The *in vivo* levels of matrix metalloproteinase-1 and -8 in gingival crevicular fluid during initial orthodontic tooth movement. *Journal of Dental Research* 82: 1018–1022
- Bakker A D, Joldersma M, Klein-Nulend J, Burger E H 2003 Interactive effects of PTH and mechanical stress on nitric oxide and PGE₂ production by primary mouse osteoblastic cells. *American Journal of Physiology. Endocrinology and Metabolism* 285: E608–E613
- Banes A J, Gilbert J, Taylor D, Monbureau O 1985 A new vacuum-operated stress-providing instrument that applies static or variable duration cyclic tension or compression to cells *in vitro*. *Journal of Cell Science* 75: 35–42
- Beertsen W, McCulloch C A, Sodek J 1997 The periodontal ligament: a unique, multifunctional connective tissue. *Periodontology* 2000 13: 20–40
- Binderman I, Bahar H, Yaffe A 2002 Strain relaxation of fibroblasts in the marginal periodontium is the common trigger for alveolar bone resorption: a novel hypothesis. *Journal of Periodontology* 73: 1210–1215
- Birkedal-Hansen H *et al.* 1993 Matrix metalloproteinases: a review. *Critical Reviews in Oral Biology and Medicine* 4: 197–250
- Brand R A, Stanford C M, Nicoletta D P 2001 Primary adult human bone cells do not respond to tissue (continuum) level strains. *Journal of Orthopaedic Science* 6: 295–301
- Brudvik P, Rygh P 1994 Multi-nucleated cells remove the main hyalinized tissue and start resorption of adjacent root surfaces. *European Journal of Orthodontics* 16: 265–273
- Bumann A, Carvalho R S, Schwarzer C L, Yen E H 1997 Collagen synthesis from human PDL cells following orthodontic tooth movement. *European Journal of Orthodontics* 19: 29–37
- Burger E H, Klein-Nulend J, Smit T H 2003 Strain-derived canalicular fluid flow regulates osteoclast activity in a remodelling osteon—a proposal. *Journal of Biomechanics* 36: 1453–1459
- Cattaneo P M, Dalstra M, Melsen B 2005 The finite element method: a tool to study orthodontic tooth movement. *Journal of Dental Research* 84: 428–433
- Cheng H *et al.* 2003 Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). *Journal of Bone and Joint Surgery* 85A: 1544–1552
- Cherian P P *et al.* 2005 Mechanical strain opens connexin 43 hemichannels in osteocytes: a novel mechanism for the release of prostaglandin. *Molecular Biology of the Cell* 16: 3100–3106
- Chiba M, Komatsu K 1993 Mechanical responses of the periodontal ligament in the transverse section of the rat mandibular incisor at various velocities of loading *in vitro*. *Journal of Biomechanics* 26: 561–570
- Clark W D, Smith E L, Linn K A, Paul-Murphy J R, Muir P, Cook M E 2005 Osteocyte apoptosis and osteoclast presence in chicken radii 0–4 days following osteotomy. *Calcified Tissue International* 77: 327–336
- Cowin S C, Weinbaum S, Zeng Y 1995 A case for bone canaliculi as the anatomical site of strain generated potentials. *Journal of Biomechanics* 28: 1281–1297
- Cronau M, Ihlow D, Kubein-Meesenburg D, Fanghanel J, Dathe H, Nagerl H 2006 Biomechanical features of the periodontium: an experimental pilot study *in vivo*. *American Journal of Orthodontics and Dentofacial Orthopedics* 129: 599.e513–599.e521
- Davidovitch Z 1991 Tooth movement. *Critical Reviews in Oral Biology and Medicine* 2: 411–450
- Davidovitch Z, Nicolay O F, Ngan P W, Shanfeld J L 1988 Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. *Dental Clinics of North America* 32: 411–435
- Dereka X E, Markopoulou C E, Vrotsos I A 2006 Role of growth factors on periodontal repair. *Growth Factors* 24: 260–267
- Duncan R L, Turner C H 1995 Mechanotransduction and the functional response of bone to mechanical strain. *Calcified Tissue International* 57: 344–358
- Gay C V, Weber J A 2000 Regulation of differentiated osteoclasts. *Critical Reviews in Eukaryotic Gene Expression* 10: 213–230
- Goldmann W H 2002 Mechanical aspects of cell shape regulation and signaling. *Cell Biology International* 26: 313–317
- Harter L V, Hruska K A, Duncan R L 1995 Human osteoblast-like cells respond to mechanical strain with increased bone matrix protein production independent of hormonal regulation. *Endocrinology* 136: 528–535
- Hill P A 1998 Bone remodelling. *British Journal of Orthodontics* 25: 101–107
- Howard P S, Kucich U, Taliwal R, Korostoff J M 1998 Mechanical forces alter extracellular matrix synthesis by human periodontal ligament fibroblasts. *Journal of Periodontal Research* 33: 500–508
- Hynes R O 1992 Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 69: 11–25
- Ingman T, Apajalahti S, Mantyla P, Savolainen P, Sorsa T 2005 Matrix metalloproteinase-1 and -8 in gingival crevicular fluid during orthodontic tooth movement: a pilot study during 1 month of follow-up after fixed appliance activation. *European Journal of Orthodontics* 27: 202–207
- Iwasaki L R, Haack J E, Nickel J C, Reinhardt R A, Petro T M 2001 Human interleukin-1 beta and interleukin-1 receptor antagonist secretion and velocity of tooth movement. *Archives of Oral Biology* 46: 185–189
- Kimmel D B 1993 A paradigm for skeletal strength homeostasis. *Journal of Bone and Mineral Research* 8 (supplement 2): S515–S522
- Kingsley N W 1980 Treatise on oral deformities as a branch of mechanical surgery. Appleton, New York
- Klein-Nulend J, Roelofs J, Sterck J G, Semeins C M, Burger E H 1995a Mechanical loading stimulates the release of transforming growth factor-beta activity by cultured mouse calvariae and periosteal cells. *Journal of Cellular Physiology* 163: 115–119

- Klein-Nulend J, Semeins C M, Ajubi N E, Nijweide P J, Burger E H 1995b Pulsating fluid flow increases nitric oxide (NO) synthesis by osteocytes but not periosteal fibroblasts—correlation with prostaglandin upregulation. *Biochemical and Biophysical Research Communications* 217: 640–648
- Klein-Nulend J *et al.* 1995c Sensitivity of osteocytes to biomechanical stress *in vitro*. *The FASEB Journal* 9: 441–445
- Knothe Tate M L, Steck R, Forwood M R, Niederer P 2000 *In vivo* demonstration of load-induced fluid flow in the rat tibia and its potential implications for processes associated with functional adaptation. *Journal of Experimental Biology* 203: 2737–2745
- Komatsu K, Kanazashi M, Shimada A, Shibata T, Viidik A, Chiba M 2004 Effects of age on the stress-strain and stress-relaxation properties of the rat molar periodontal ligament. *Archives of Oral Biology* 49: 817–824
- Krishnan V, Davidovitch Z 2006 Cellular, molecular, and tissue-level reactions to orthodontic force. *American Journal of Orthodontics and Dentofacial Orthopedics* 129: 469.e1–469.e32
- Kurata K, Heino T J, Higaki H, Vaananen H K 2006 Bone marrow cell differentiation induced by mechanically damaged osteocytes in 3D gel-embedded culture. *Journal of Bone and Mineral Research* 21: 616–625
- Langholz O *et al.* 1995 Collagen and collagenase gene expression in three-dimensional collagen lattices are differentially regulated by alpha 1 beta 1 and alpha 2 beta 1 integrins. *Journal of Cell Biology* 131: 1903–1915
- Mak A F, Huang D T, Zhang J D, Tong P 1997 Deformation-induced hierarchical flows and drag forces in bone canaliculi and matrix microporosity. *Journal of Biomechanics* 30: 11–18
- Masella R S, Meister M 2006 Current concepts in the biology of orthodontic tooth movement. *American Journal of Orthodontics and Dentofacial Orthopedics* 129: 458–468
- Matsuda N, Morita N, Matsuda K, Watanabe M 1998 Proliferation and differentiation of human osteoblastic cells associated with differential activation of MAP kinases in response to epidermal growth factor, hypoxia, and mechanical stress *in vitro*. *Biochemical and Biophysical Research Communications* 249: 350–354
- Meikle M C 2006 The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt. *European Journal of Orthodontics* 28: 221–240
- Melsen B 1999 Biological reaction of alveolar bone to orthodontic tooth movement. *Angle Orthodontist* 69: 151–158
- Melsen B 2001 Tissue reaction to orthodontic tooth movement—a new paradigm. *European Journal of Orthodontics* 23: 671–681
- Mori S, Burr D B 1993 Increased intracortical remodeling following fatigue damage. *Bone* 14: 103–109
- Mullender M G, Huiskes R 1995 Proposal for the regulatory mechanism of Wolff's law. *Journal of Orthopaedic Research* 13: 503–512
- Mullender M, El Haj A J, Yang Y, van Duin M A, Burger E H, Klein-Nulend J 2004 Mechanotransduction of bone cells *in vitro*: mechanobiology of bone tissue. *Medical & Biological Engineering & Computing* 42: 14–21
- Nahm D S, Kim H J, Mah J, Baek S H 2004 *In vitro* expression of matrix metalloproteinase-1, tissue inhibitor of metalloproteinase-1 and transforming growth factor-beta1 in human periodontal ligament fibroblasts. *European Journal of Orthodontics* 26: 129–135
- Nakagawa M, Kukita T, Nakasima A, Kurisu K 1994 Expression of the type I collagen gene in rat periodontal ligament during tooth movement as revealed by *in situ* hybridization. *Archives of Oral Biology* 39: 289–294
- Nakamura K, Sahara N, Deguchi T 2001 Temporal changes in the distribution and number of macrophage-lineage cells in the periodontal membrane of the rat molar in response to experimental tooth movement. *Archives of Oral Biology* 46: 593–607
- Natali A N, Pavan P G, Scarpa C 2004 Numerical analysis of tooth mobility: formulation of a non-linear constitutive law for the periodontal ligament. *Dental Materials* 20: 623–629
- Noble B 2005 Microdamage and apoptosis. *European Journal of Morphology* 42: 91–98
- Noble B S, Stevens H, Loveridge N, Reeve J 1997 Identification of apoptotic changes in osteocytes in normal and pathological human bone. *Bone* 20: 273–282
- Noble B S *et al.* 2003 Mechanical loading: biphasic osteocyte survival and targeting of osteoclasts for bone destruction in rat cortical bone. *American Journal of Physiology. Cell Physiology* 284: C934–C943
- Nomura S, Takano-Yamamoto T 2000 Molecular events caused by mechanical stress in bone. *Matrix Biology* 19: 91–96
- Okumura E 1982 Light and electron microscopic study of multinucleated giant cells related with the resorption of hyalinized tissues. *Nippon Kyosei Shika Gakkai Zasshi* 41: 531–555
- Oshiro T, Shiotani A, Shibasaki Y, Sasaki T 2002 Osteoclast induction in periodontal tissue during experimental movement of incisors in osteoprotegerin-deficient mice. *The Anatomical Record* 266: 218–225
- Owan I *et al.* 1997 Mechanotransduction in bone: osteoblasts are more responsive to fluid forces than mechanical strain. *American Journal of Physiology* 273: C810–C815
- Ozaki S, Kaneko S, Podyma-Inoue K A, Yanagishita M, Soma K 2005 Modulation of extracellular matrix synthesis and alkaline phosphatase activity of periodontal ligament cells by mechanical stress. *Journal of Periodontal Research* 40: 110–117
- Phan T C, Xu J, Zheng M H 2004 Interaction between osteoblast and osteoclast: impact in bone disease. *Histology and Histopathology* 19: 1325–1344
- Pilon J J 1996 Orthodontic forces and tooth movement, an experimental study in beagle dogs. Thesis, University of Nijmegen
- Pitsillides A A, Rawlinson S C, Suswillo R F, Bourrin S, Zaman G, Lanyon L E 1995 Mechanical strain-induced NO production by bone cells: a possible role in adaptive bone (re)modeling?. *The FASEB Journal* 9: 1614–1622
- Proffit W R 2000 Contemporary orthodontics. Mosby, St Louis
- Reitan K 1951 The initial tissue reaction incident to orthodontic tooth movement as related to the influence of function; an experimental histologic study on animal and human material. *Acta Odontologica Scandinavica. Supplementum* 6: 1–240
- Rygh P 1973 Ultrastructural changes in pressure zones of human periodontium incident to orthodontic tooth movement. *Acta Odontologica Scandinavica* 31: 109–122
- Rygh P, Bowling K, Hovlandsdal L, Williams S 1986 Activation of the vascular system: a main mediator of periodontal fiber remodeling in orthodontic tooth movement. *American Journal of Orthodontics* 89: 453–468
- Sasano T, Kuriwada S, Sanjo D, Izumi H, Tabata T, Karita K 1992 Acute response of periodontal ligament blood flow to external force application. *Journal of Periodontal Research* 27: 301–304
- Shiotani A, Shibasaki Y, Sasaki T 2001 Localization of receptor activator of NF-kappaB ligand, RANKL, in periodontal tissues during experimental movement of rat molars. *Journal of Electron Microscopy* 50: 365–369
- Singhatanadgit W, Salih V, Olsen I 2006 Up-regulation of bone morphogenetic protein receptor IB by growth factors enhances BMP-2-induced human bone cell functions. *Journal of Cellular Physiology* 209: 912–922
- Snoek-van Beurden P A, Von den Hoff J W 2005 Zymographic techniques for the analysis of matrix metalloproteinases and their inhibitors. *BioTechniques* 38: 73–83
- Takahashi I, Onodera K, Nishimura M, Mitnai H, Sasano Y, Mitani H 2006 Expression of genes for gelatinases and tissue inhibitors of metalloproteinases in periodontal tissues during orthodontic tooth movement. *Journal of Molecular Biology* 37: 333–342
- Takahashi I *et al.* 2003 Expression of MMP-8 and MMP-13 genes in the periodontal ligament during tooth movement in rats. *Journal of Dental Research* 82: 646–651
- Tan S D *et al.* 2006 Fluid shear stress inhibits TNFalpha-induced osteocyte apoptosis. *Journal of Dental Research* 85: 905–909
- Tang L, Lin Z, Li Y M 2006 Effects of different magnitudes of mechanical strain on osteoblasts *in vitro*. *Biochemical and Biophysical Research Communications* 344: 122–128

- Taylor D, Lee T C 2003 Microdamage and mechanical behaviour: predicting failure and remodelling in compact bone. *Journal of Anatomy* 203: 203–211
- Teitelbaum S L, Tondravi M M, Ross F P 1997 Osteoclasts, macrophages, and the molecular mechanisms of bone resorption. *Journal of Leukocyte Biology* 61: 381–388
- Terai K *et al.* 1999 Role of osteopontin in bone remodeling caused by mechanical stress. *Journal of Bone and Mineral Research* 14: 839–849
- Theoleyre S, Wittrant Y, Tat S K, Fortun Y, Redini F, Heymann D 2004 The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. *Cytokine and Growth Factor Reviews* 15: 457–475
- Turner R T, Evans G L, Wakley G K 1995 Spaceflight results in depressed cancellous bone formation in rat humeri. *Aviation, Space, and Environmental Medicine* 66: 770–774
- Uematsu S, Mogi M, Deguchi T 1996a Increase of transforming growth factor-beta 1 in gingival crevicular fluid during human orthodontic tooth movement. *Archives of Oral Biology* 41: 1091–1095
- Uematsu S, Mogi M, Deguchi T 1996b Interleukin (IL)-1 beta, IL-6, tumor necrosis factor-alpha, epidermal growth factor, and beta 2-microglobulin levels are elevated in gingival crevicular fluid during human orthodontic tooth movement. *Journal of Dental Research* 75: 562–567
- van der Pauw M T, Klein-Nulend J, van den Bos T, Burger E H, Everts V, Beertsen W 2000 Response of periodontal ligament fibroblasts and gingival fibroblasts to pulsating fluid flow: nitric oxide and prostaglandin E₂ release and expression of tissue non-specific alkaline phosphatase activity. *Journal of Periodontal Research* 35: 335–343
- van Driel W D, van Leeuwen E J, Von den Hoff J W, Maltha J C, Kuijpers-Jagtman A M 2000 Time-dependent mechanical behaviour of the periodontal ligament. *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine* 214: 497–504
- Verna C, Dalstra M, Lee T C, Cattaneo P M, Melsen B 2004 Microcracks in the alveolar bone following orthodontic tooth movement: a morphological and morphometric study. *European Journal of Orthodontics* 26: 459–467
- Verstappen J, Von den Hoff J W 2006 Tissue inhibitors of metalloproteinases (TIMPs): their biological functions and involvement in oral disease. *Journal of Dental Research* 85: 1074–1084
- Von den Hoff J W 2003 Effects of mechanical tension on matrix degradation by human periodontal ligament cells cultured in collagen gels. *Journal of Periodontal Research* 38: 449–457
- Wall M E, Banes A J 2005 Early responses to mechanical load in tendon: role for calcium signaling, gap junctions and intercellular communication. *Journal of Musculoskeletal and Neuronal Interactions* 5: 70–84
- Wang J H, Thampatty B P 2006 An introductory review of cell mechanobiology. *Biomechanics and Modeling in Mechanobiology* 5: 1–16
- Wang L L, Zhu H, Liang T 2000 Changes of transforming growth factor beta 1 in rat periodontal tissue during orthodontic tooth movement. *Chinese Journal of Dental Research* 3: 19–22
- Weinbaum S, Cowin S C, Zeng Y 1994 A model for the excitation of osteocytes by mechanical loading-induced bone fluid shear stresses. *Journal of Biomechanics* 27: 339–360
- Westbroek I *et al.* 2000 Differential stimulation of prostaglandin G/H synthase-2 in osteocytes and other osteogenic cells by pulsating fluid flow. *Biochemical and Biophysical Research Communications* 268: 414–419
- Xu J, Clark R A F 1996 Extracellular matrix alters PDGF regulation of fibroblast integrins. *Journal of Cell Biology* 132: 239–249
- Yamaguchi M *et al.* 2004 Cathepsins B and L increased during response of periodontal ligament cells to mechanical stress *in vitro*. *Connective Tissue Research* 45: 181–189
- Yang Y Q, Li X T, Rabie A B, Fu M K, Zhang D 2006 Human periodontal ligament cells express osteoblastic phenotypes under intermittent force loading *in vitro*. *Frontiers in Bioscience* 11: 776–781
- Yoo S K, Warita H, Soma K 2004 Duration of orthodontic force affecting initial response of nitric oxide synthase in rat periodontal ligaments. *Journal of Medical and Dental Sciences* 51: 83–88
- Yoshida N, Jost-Brinkmann P G, Koga Y, Mimaki N, Kobayashi K 2001 Experimental evaluation of initial tooth displacement, center of resistance, and center of rotation under the influence of an orthodontic force. *American Journal of Orthodontics and Dentofacial Orthopedics* 120: 190–197
- You J, Yellowley C E, Donahue H J, Zhang Y, Chen Q, Jacobs C R 2000 Substrate deformation levels associated with routine physical activity are less stimulatory to bone cells relative to loading-induced oscillatory fluid flow. *Journal of Biomechanical Engineering* 122: 387–393
- Zhao S, Zhang Y K, Harris S, Ahuja S S, Bonewald L F 2002 MLO-Y4 osteocyte-like cells support osteoclast formation and activation. *Journal of Bone and Mineral Research* 17: 2068–2079

Copyright of European Journal of Orthodontics is the property of Oxford University Press / UK and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.