Bone regeneration during distraction osteogenesis: Mechano-regulation by shear strain and fluid velocity

Hanna Isaksson\textsuperscript{a,b}, Olivier Comas\textsuperscript{b}, Corrinus C. van Donkelaar\textsuperscript{b}, Jesus Mediavilla\textsuperscript{b}, Wouter Wilson\textsuperscript{b}, Rik Huiskes\textsuperscript{b,c}, Keita Ito\textsuperscript{a,b,*}

\textsuperscript{a}AO Research Institute, Clavadelerstrasse 8, 7270 Davos Platz, Switzerland
\textsuperscript{b}Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands
\textsuperscript{c}Department of Orthopaedics, University of Maastricht, The Netherlands

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Abstract

Corroboration of mechano-regulation algorithms is difficult, partly because repeatable experimental outcomes under a controlled mechanical environment are necessary, but rarely available. In distraction osteogenesis (DO), a controlled displacement is used to regenerate large volumes of new bone, with predictable and reproducible outcomes, allowing to computationally study the potential mechanisms that stimulate bone formation. We hypothesized that mechano-regulation by octahedral shear strain and fluid velocity can predict the spatial and temporal tissue distributions seen during experimental DO. Variations in predicted tissue distributions due to alterations in distraction rate and frequency could then also be studied. An in vivo ovine tibia experiment evaluating bone-segment transport (distraction, 1 mm/day) over an intramedullary nail was used for comparison. A 2D axisymmetric finite element model, with a geometry originating from the experimental data, was created and included into a previously developed model of tissue differentiation. Cells migrated and proliferated into the callus, differentiating into fibroblasts, chondrocytes or osteoblasts, dependent on the biophysical stimuli. Matrix production was modelled with an osmotic swelling model to allow tissues to grow at individual rates. The temporal and spatial tissue distributions predicted by the computational model agreed well with those seen experimentally. In addition, it was observed that decreased distraction rate (0.5 mm/d vs. 0.25 mm/d) increased the overall time needed for complete bone regeneration, whereas increased distraction frequency (0.5 mm/12 h vs. 0.25 mm/6 h) stimulated faster bone regeneration, as found in experimental findings by others. Thus, the algorithm regulated by octahedral shear strain and fluid velocity was able to predict the bone regeneration patterns dependent on distraction rate and frequency during DO.

Keywords: Tissue differentiation; Mechanobiology; Finite-element analysis; Tissue growth; Bone-segment transport

1. Introduction

Osteogenesis has frequently been studied experimentally and computationally. In osteogenesis, associated differentiation of precursor cells is sensitive to the local mechanical environment. There have been several propositions of how this is mechano-regulated. However, corroboration of these algorithms are difficult (Isaksson et al., 2006a), mostly because repeatable experimental outcomes under controlled mechanical environments are required, but rarely available in experimental or clinical studies.

Distraction osteogenesis (DO) is a procedure by which controlled displacement of a bone fragment is used to generate large volumes of new bone that have been lost due to trauma, infection or tumour resection (Ilizarov, 1989a; Richards et al., 1998). It can also be used to correct a variety of orthopaedic deformities and malformations. The outcome is predictable and reproducible. Therefore, it is a suitable model for studying the potential mechanisms that stimulate bone formation and for examining the role of mechanical forces. DO is usually separated into three
phases. The first is the latency phase, immediately following osteotomy before distraction. The second is the distraction phase in which there is active distraction of the bony segments for a certain time at specific rates (total distance/day and frequencies (number of distractions/day). During this period, tissue differentiation is initiated, with some sparse bone formation. The third is the consolidation phase, during which there is no distraction, which finally leads to bone union. The rate of bone formation during DO is directly related to the distraction rate (Ilizarov, 1989b; Li et al., 1999, 2000), frequency (Aarnes et al., 2002; Ilizarov, 1989b; Mizuta et al., 2003) and the strain/stress generated in the distraction gap (Li et al., 1997, 1999). Meyer et al. (2001a) showed that the magnitude of distraction-generated mechanical tension directly influenced the phenotypic differentiation of the cells within the distraction gap.

Although DO provides an attractive setting for the study of mechanical effects on bone regeneration, very little computational evaluation has been performed. Morgan et al. (2006) investigated the local physical environment within an osteotomy gap during long bone DO and correlated tissue dilatation (volumetric strain) with differentiation of mesenchymal tissue. They evaluated distraction and tissue relaxation during one single day of the distraction period. Loboa et al. (2005) used finite-element (FE) analysis to correlate bone formation with magnitudes of tensile strain and hydrostatic pressure (Carter et al., 1998) during mandibular DO at four time points. So far no studies have described the process of tissue differentiation during DO both spatially and temporally during the complete distraction process. This type of computational evaluation of DO will provide useful information about the local stress and strain magnitudes that lead to the highest amount of bone regeneration, and enable optimization of treatments.

The mechano-regulation algorithm based on octahedral shear strain and fluid velocity was proposed by Prendergast et al. (1997) as a general tissue differentiation scheme. The threshold values for this algorithm were initially determined to predict bone formation around implants (Huiskes et al., 1997). Thereafter it has been shown to predict tissue differentiation during secondary fracture healing (Lacroix and Prendergast, 2002; Lacroix et al., 2002; Isaksson et al., 2006b), in bone chambers (Geris et al., 2003, 2004) and during osteochondral defect repair (Kelly and Prendergast, 2005). Recently, we demonstrated that it was more consistent with bone healing under both shear and compressive deformations (Isaksson et al., 2006a) than other algorithms (Carter et al., 1998; Claes and Heigele, 1999; Isaksson et al., 2006b).

During DO the tissue is subjected to tension, a mechanical mode for which this algorithm has never been tested. For this study, we hypothesized that mechano-regulation by octahedral shear strain and fluid velocity can also predict spatial and temporal tissue distributions seen experimentally during DO, including variations due to alteration in distraction rate and frequency.

2. Methods

2.1. Experimental model

Data from an ovine in vivo experiment for evaluation of bone segment transport over an intramedullary nail, previously conducted in our institution, was used for comparison (Brunner et al., 1993, 1994). A distal diaphyseal defect, either 20 or 45 mm, was created in the left tibia. The tibia was then stabilized with an unreamed static interlocking nail. After corticotomy, bone segments were transported (distracted) using subcutaneous traction wires over the nail (Fig. 1(a)). Distraction started on post-operative day 1 with a rate of 1 mm/d until the defect was closed, followed by consolidation. Animals were sacrificed after 12 weeks for the short defects and 16 weeks for the long defects. Daily distraction forces were measured before (resting force), during (peak force) and 5 min after distraction. The resting force represented the tension between the distracted segment and the fixator before distraction. The peak force was the sum of all forces between fixator and distracted segment after 1 mm distraction. The relaxation behaviour was calculated as the difference between resting force and peak force, divided by the peak force, and was used as a measure of the viscoelasticity of the tissue. Weekly standardized radiographs and undecalcified histology at the time of completed transport were available for comparison.

2.2. FE model

A 2D axisymmetric FE mesh was created based on the geometry of the tibia, the nail and the callus from the experimental data (Brunner et al., 1994) (Fig. 1(b)). The initial corticotomy gap was set to 1 mm. Boundary conditions were applied according to the experimental model. The ends of bone and marrow and the external callus boundary were assumed impermeable. Distraction (1 mm/d for 20 or 45 d) was applied to the top of the cortical bone and started on post-operative day 1. Distraction was followed by consolidation, where no active mechanical stimulation was applied, according to the experimental protocol. Each iteration simulated 1 d, where distraction was performed over 1 s followed by 24 h of relaxation, during which reaction forces were monitored. All tissues were assumed to follow linear poroelasticity theory with properties taken from literature (Table 1). The intramedullary nail was assumed to be rigid compared to the biological tissues and the interfaces between the nail and the tissues were modelled using finite sliding and zero friction (ABAQUS, v 6.5, ABAQUS Inc. Pawtucket, RI, USA).

![Fig. 1. Experimental and computational model. (a) The experimental model from Brunner et al. (1994) including initial defect and corticotomy, followed by a distraction phase (bone segment transport) and final consolidation period. (b) The initial two-dimensional axisymmetric finite element model was created from the experimental measurements. The initial gap size was 1 mm. The nail diameter was 7 mm, the cortical bone’s inner diameter 14 mm, and outer diameter 20 mm.](image)
Table 1
Material properties used to describe the tissues in this study

<table>
<thead>
<tr>
<th>Material</th>
<th>Cortical bone</th>
<th>Marrow</th>
<th>Granulation tissue</th>
<th>Fibrous tissue</th>
<th>Cartilage</th>
<th>Immature bone</th>
<th>Mature bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young’s modulus (MPa)</td>
<td>15750(^a)</td>
<td>2</td>
<td>1</td>
<td>2(^b)</td>
<td>10(^i)</td>
<td>1000</td>
<td>6000(^d)</td>
</tr>
<tr>
<td>Permeability (m(^2)/Ns)</td>
<td>1E-17(^c)</td>
<td>1E-14</td>
<td>1E-14</td>
<td>1E-14(^h)</td>
<td>5E-15(^f)</td>
<td>1E-13</td>
<td>3.7E-13(^e)</td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td>0.325(^b)</td>
<td>0.167</td>
<td>0.167</td>
<td>0.167</td>
<td>0.167(^j)</td>
<td>0.325</td>
<td>0.325</td>
</tr>
<tr>
<td>Solid bulk modulus (MPa)</td>
<td>17 660(^d)</td>
<td>2300</td>
<td>2300</td>
<td>2300(^i)</td>
<td>3400(^k)</td>
<td>17 660(^m)</td>
<td>17 660(^n)</td>
</tr>
<tr>
<td>Fluid bulk modulus (MPa)</td>
<td>2300</td>
<td>2300</td>
<td>2300</td>
<td>2300</td>
<td>2300</td>
<td>2300</td>
<td>2300</td>
</tr>
<tr>
<td>Porosity</td>
<td>0.04(^l)</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

\(^{a}\) (Smit et al., 2002), \(^{b}\) (Hori and Lewis, 1982), \(^{c}\) (Lacroix and Prendergast, 2002), \(^{d}\) (Claes and Heigele, 1999), \(^{e}\) (Johnson et al., 1982), \(^{f}\) (Armstrong and Mow, 1982), \(^{g}\) (Cowin, 1999), \(^{h}\) (Jurvelin et al., 1997), \(^{i}\) (Anderson, 1967), \(^{j}\) (Tepic et al., 1983), \(^{k}\) (Schaffler and Burr, 1988), \(^{l}\) (Mow et al., 1980).

2.3. Adaptive tissue differentiation model

The adaptive tissue differentiation process was accomplished through custom-written subroutines (MATLAB, The Mathworks Inc. v. 7.1) (Fig. 2) and based on an earlier adaptive model (Isaksson et al., 2006b). The meshing of the callus was performed by an automatic meshing algorithm into triangular elements, which were transformed into quadrilateral elements with a maximum area of 0.1 mm\(^2\) for the FE analysis (Brokken, 1999). The initial corticotomy consisted of granulation tissue, without any precursor cells. The precursor cells could then migrate into the callus from the boundaries between callus, marrow and periosteum, at an unlimited supply. This was simulated as a diffusive process to incorporate migration and proliferation of cells (Lacroix et al., 2002; Isaksson et al., 2006b). The distraction was applied and the biophysical stimuli were calculated in the FE analysis at maximal distraction. The new tissue phenotypes were predicted according to the local magnitudes of octahedral shear strain and fluid velocity (Prendergast et al., 1997). The cells within an element of callus tissue were able to differentiate into fibroblasts, chondrocytes or osteoblasts and to produce their respective matrices. Cell differentiation and the type of matrix produced by the present cells were only restricted by the mechanical environment. The differentiation of the cells between one phenotype and another was not explicitly modelled, but by having the type of matrix modulated by the mechanical environment, tissue transformation over time and space was modelled. There was one additional requisite that bone was only allowed to form on already calcified surfaces (Claes and Heigele, 1999).

Matrix production of different tissue types was modelled to occur separately, at individual rates, depending on cell type and cell density. Matrix production and growth were simulated by applying a swelling pressure to the growing element and considering the subsequent volume expansion as being an increase in matrix. The biphasic swelling model of Wilson et al. (2005) was adopted for this growth simulation. In this model swelling pressure is given by

$$\Delta p = RT(\sqrt{c_F^2 + 4c_{\text{ext}}^2} - 2c_{\text{ext}}),$$

(1)

where \(R\) is the gas constant, \(T\) the absolute temperature, \(c_{\text{ext}}\) the external salt concentration and \(c_F\) the fixed charged density which can be expressed as a function of the tissue deformation as

$$c_F = c_{F,0} \left(\frac{n_{i,0}}{c_{F,0} - 1 + J}\right),$$

(2)

where \(n_{i,0}\) is the initial fluid fraction of the tissue, \(c_{F,0}\) the initial amount of negative charges in the tissue and \(J\) the determinant of the deformation tensor. Before a simulation, all negative charges were set to zero and the displaced geometry after the previous distraction served as input. Identical geometrical boundary conditions were applied. Growth was induced by introducing a non-zero amount of fixed charges in the growing element, dependent on the cell type simulated in the element (Table 2). The fixed-charge density changes were chosen such that they resulted in growth/volume changes within the range of those found experimentally for each

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Table 2
Material properties and constants used in the osmotic swelling model to predict tissue growth

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>(n_{i,0})</th>
<th>(c_{F,i,0}) (meq/mm³)</th>
<th>Resulting growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous tissue</td>
<td>0.8</td>
<td>(7 \times 10^{-2})</td>
<td>~15–20%</td>
</tr>
<tr>
<td>Cartilage</td>
<td>0.8</td>
<td>(3.5 \times 10^{-2})</td>
<td>~5–7%</td>
</tr>
<tr>
<td>Appositional bone growth</td>
<td>0.8</td>
<td>(3.5 \times 10^{-2})</td>
<td>~5 μm/d(^a)</td>
</tr>
<tr>
<td>Endochondral bone growth</td>
<td>0.8</td>
<td>(5.25 \times 10^{-2})</td>
<td>~25 μm/d(^b)</td>
</tr>
</tbody>
</table>

The assumed fluid fraction \(n_{i,0}\) and the fixed charged density \(c_{F,i,0}\) are inputs and the volume growth and bone growth rate are the calculated growth of the various tissue types.

\(^a\)(Eriksen et al., 1984; Vedi et al., 2005).

\(^b\)(Wilsman et al., 1996a, b).

The experimental results, published in detail elsewhere, showed good reproducibility (Brunner et al., 1993, 1994). Post-operatively there was a narrow corticotomy gap. During the first week of distraction ‘graining’ appeared, i.e. small slightly radio-opaque areas appeared throughout the distraction gap without any organized pattern. From the second week of distraction, strips of increased radio-opacity were running from the two cortical bone ends and growing towards each other. A small overlapping callus on the periosteal side was observed. Furthermore the observed bone growth was more substantial on the periosteal side compared to the endosteal side and the nail interface. During distraction of the segment, bone formation was clearly observed in the longitudinal direction of distraction, particularly with the larger defect size, with increasing density over time, and with highest density closer to the cortical ends, where the initial bone formation was seen. Throughout continued distraction of the bone fragment an area of soft tissue was located in the middle of the regenerate. During consolidation, reorganization and maturation of regenerated bone occurred. Over time, the soft tissue gap diminished and bony bridging occurred. In general the same patterns were observed in the short and long regenerates, but in the long ones, the different stages of healing were more clearly distinguished.

3. Results

The predicted tissue distributions agreed well with those seen experimentally (Fig. 3). During the first week, the mesenchymal stem cells that migrated and proliferated into the callus mainly differentiated into fibroblasts. Thus, the predicted tissue distributions were primarily fibrous tissue. After 7 d, differentiation into...
osteoblasts was first observed along the periosteum and in the gap area (Fig. 3(b), iteration (it) 10). After 15 d bone tissue could be distinguished close to the periosteum. During distraction of the segment, bone continued to develop. Slow creeping substitution of bone was seen in the longitudinal direction of distraction, with a higher density at the periosteal side (Fig. 3(a), it 35). Throughout distraction of the bone segment, there was a gap of soft tissue in-between the bony ends, which reached a steady size between day 30 and 40. The predicted areas of bone mainly remained immature until distraction was finalized. During consolidation, maturation of the bone occurred followed by final bony bridging. Similar distributions and stages of tissue differentiation were seen for both defect sizes (both in simulations and experiments), but the continued bone growth during distraction was mainly seen in the longer defects.

Reaction forces and relaxation behaviour were also compared. Reaction forces increased almost linearly during the first weeks of distraction in the experiment with a temporary drop in the rate of increase during the third week in four out of five sheep (Fig. 4(a)) (Brunner et al., 1994). Computationally, the peak force was initially higher than experimentally found and over time it decreased slightly due to the increased soft tissue regenerate (Fig. 4(a)). Predicted relaxation forces compared well with the experiments (Fig. 4(b)). The stress relaxation curves of the tissues during transport were initially between 60% and 70% in the experiment, compared to 65% computationally. During distraction the relaxation increased to about 80% for both experimental results and the computational prediction (Fig. 4(b)).

When the distraction rate was decreased to 0.5 mm/d or 0.25 mm/d the total time for bone regeneration increased, even though the amount of bone formation at the same magnitude of total distraction increased with decreasing rate (Fig. 5). When the distraction frequency increased to 0.5 mm distraction two times/day, or 0.25 mm distraction four times/day, the overall rate of bone formation increased (Fig. 6). During the first week of distraction the tissue distributions were similar and mainly fibrous for all three frequencies, but as distraction proceeded into the second and third week the amount of bone formation increased with the frequency. Also the consolidation period necessary to achieve complete bridging became shorter with increased distraction frequency.

4. Discussion

A mechano-regulation algorithm based on octahedral shear strain and fluid flow was able to predict the bone formation pattern observed experimentally during DO from initial corticotomy to final consolidation. The comparison of spatial and temporal patterns of bone regeneration was successful. The first bone formation was seen in the cortical gap at the end of week two of

Fig. 3. Tissue differentiation during distraction of the long defects followed by consolidation. Distraction rate and frequency are identical to the experimental study, i.e. 1 mm/d distracted once. (a) Predicted bone regeneration pattern. The tissue type was based on the average element moduli as determined by the mixture theory (Eqs. (3)-(5)). (b) Stimulated cell types.
distraction in both experiments and predictions. These events were followed by progressive bone growth in the direction of distraction, with increased bone density at the periosteal side. Areas of soft tissue remaining in the gap throughout distraction of the segment, and bone maturation seen during consolidation, were similar in both experiment and computational predictions. The mechano-regulation algorithm has previously been shown suitable to predict fracture healing, as well as other bone regenerative processes. Now it has been taken one step further, by successfully predicting the bone formation patterns during DO.

During DO the tissue is subjected to tension, in contrast to fracture healing where compression is predominant. With tensile loads, for example, the fluid velocity is directionally reversed, when compared to compressive loading. The mechano-regulation algorithm only considers the magnitude of the fluid velocity, and not the direction. Hence, in terms of the mechano-regulation algorithm, the loading conditions are not very different. The magnitudes of the two stimuli after distraction are displayed in Fig. 7. Furthermore, the relaxation behaviour over 24 h is shown. This confirms that the peak values of the stimuli indeed occur around the time of maximal distraction. The

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magnitudes of fluid velocity decreased rapidly as soon as distraction was completed (Fig. 7(c)), while the deviatoric strain remained high during the beginning of the relaxation period (Fig. 7(d)). Depending on the location in the callus, the strain values even slightly increased initially during relaxation. In those cases, the increases were minimal and did not affect the predicted phenotype.

The relaxation behaviour of the tissue corresponded well with what was measured experimentally. This occurs because relaxation is dominated by the modulus/permeability ratio of the callus tissue, which did not change much during the distraction period. In contrast, the reaction forces from the model did not agree with the experiment. This is probably not due to the mechano-regulation algorithm itself and the predicted pattern of tissue differentiation, but to additional factors in the experimental model that were not included in the computational model. In limb lengthening, or simple DO, there are progressively higher and higher tensions on adjacent fascia, tendons and muscles (Simpson et al., 1995; Williams et al., 1999). This is because muscles are often attached across the distraction gap. It can increase reaction forces substantially (Aronson and Harp, 1994) and also cause considerable pain for patients undergoing DO. However, in the current experimental model of bone segment transport (Brunner et al., 1994), these effects were reduced because the total length of the tibia was kept constant, and most muscles are only attached to the proximal and distal main fragments.

Still, most likely there were some contributions from the adjacent soft tissue (including muscles) on the measured forces. Hence, that is one source of discrepancy. Another probable cause for the disagreement in forces is that unlike simple DO, the segment transport model required the creation of a large gap distal to the transported segment, which would have been filled with soft tissues. With distraction of the segment, these tissues would have been compressed, eventually completely, and the compression would result in an additional force component. Finally, throughout the distraction period, with the longitudinal alignment of collagen fibers under contract traction (Meyer et al., 2001b), the modulus of the soft tissue in the gap would have increased, similar to other collagen-oriented soft tissues, e.g. fascia, vessels, etc. (Hudetz et al., 1981; Birk and Silver, 1984; Billiar and Sacks, 2000a, b). None of these effects were included in the computational model and, in combination, may be the source of discrepancy in reaction forces when compared to experimentally measured magnitudes.

Even though DO is mechanically well defined, some assumptions were necessary. The peak magnitudes of the mechanical parameters immediately after distraction were considered for the mechano-regulation, and the subsequent relaxation was assumed to have minimal mechano-biological effects. Loading during consolidation was neglected, because the performance of the algorithm during distraction (tensile displacements) was the main focus of this study.
study. Thus, the resorption criteria initially suggested for the mechano-regulation algorithm had to be excluded in this study. The nail was modelled with finite sliding and was assumed to have no influence on cell processes. This assumption was chosen since experimentally no bone formation on the nail was seen during transport. Additionally, to overcome computational difficulties with high relative strains, the initial experimental corticotomy (∼0.5 mm) was modelled as a gap of 1 mm, and the distraction rate was initially chosen 0.5 mm/d, increasing to 1 mm/d at day 3. This did not influence the tissue differentiation process since even with the lower distraction rates, fibroblasts were stimulated during this period and matrix production of fibrous tissue occurred.

Tissue growth and matrix production were modelled using a new approach. The effect of local matrix production on tissue morphology was simulated by inducing local tissue swelling in response to osmotic pressure. The parameters were chosen such that fibrous tissue would grow faster than cartilage and bone. More specifically, volume increases up to 20% occurred in the regions where fibroblasts saturated the tissue producing fibrous matrix, while the growth rate of cartilage was lower (5–10%). These relative growth rates are compatible with experimental findings. The growth during bone formation corresponded to a bone apposition rate of 5–10 μm/d (Vedi et al., 2005) and when calcification of cartilage occurred the volume growth was higher due to hypertrophy prior to mineralization (Wilsman et al., 1996a, b) and the corresponding bone formation rate was about 20 μm/d (Wilsman et al., 1996a, b). Fig. 8 displays an example of this model, where the stimulated cell types after distraction are compared with the resulting matrix production and tissue growth generated with the biphasic swelling model after 10 d of distraction. The osmotic swelling model, originally developed to describe cartilaginous tissues, was applied to compute matrix production. Hence, the concentrations of fixed charges included during matrix production are only used to achieve a new geometrical shape of the callus. The fixed charge densities and their effects on solid/fluid content in the tissue have no physical meaning and are not used in subsequent iterations. The assumption about a stress-free geometrical shape after swelling/growth was made to avoid incremental stress increases in the tissue and to allow us to use the same set of parameters to achieve the same amount of volume increase throughout the simulation. Furthermore, the relaxation times for the tissues are on the order of hours (Weiss et al., 2002; Bonifasi-Lista et al., 2005; Park and Ateshian, 2006; Huang et al., 2003). Hence, by modelling 24 h relaxation and matrix production, we believe we are well on the side where the assumption can be used. The matrix constitution in each iteration is based only on the differentiation algorithm and the rule of mixtures (Eq. (4)).

Experimental findings by others have shown that the rate of bone formation is directly related to the local strain/stress generated in the distraction gap (Li et al., 1997, 1999), and that the amount of mechanical tension directly influenced the phenotypic differentiation of the cells within the distraction gap (Meyer et al., 2001a). Our simulations with altered distraction rates agreed with these findings. When the tension in the gap was lowered by a reduction in distraction rate, the bone formation/day increased. Still, the most favourable distraction rate was 1 mm/d, because the total time needed to regenerate the bone in the defect was shorter than for lower rates. This also agrees with the findings of Ilizarov which showed 1 mm/d to be the most favourable rate. Additionally, experimental studies have shown that further increases in distraction rate can be detrimental to healing (Ilizarov, 1989b; Choi et al., 2004) and lead to a distraction gap filled with mostly fibrous tissue (Choi et al., 2004). In the current study, distraction rates above 1 mm/d were not examined. Hence, we cannot compare those experimental observations with our computational model. Ilizarov’s studies further showed that the greater the distraction frequency, the better the outcome (Ilizarov, 1989b). Our predictions demonstrated the same pattern, where the rate of bone regeneration increased with distraction frequency (Fig. 6). In our model, the best possible bone regeneration was achieved with a total distraction of 1 mm/d divided into 4 sub-distructions of 0.25 mm/6 h. Experimental studies have also suggested that the division in endochondral and intramembranous bone formation during DO is related to the distraction rate (Li et al., 1999; Mizuta et al., 2003; Kessler et al., 2005). With this model the stimulated cell phenotypes and tissue types produced were altered similarly. With a lower distraction rate the proportion of the cells that differentiated into osteoblasts without first going through a cartilage intermediate was increased.

Tissue differentiation during DO, by a mechano-regulation algorithm based on octahedral shear strain and fluid velocity, was successfully simulated from distraction to

Fig. 8. The osmotic swelling model used simulates matrix production in an element specific manner. (a) The stimulated cell phenotypes and (b) the resulting volume growth after 10 iterations with distraction rate of 1 mm/d and frequency of 1 distraction/day.
consolidation and was confirmed by experimental observations in a model of bone segment transport. The rate of bone formation depended on distraction rate and frequency, similar to experimental observations. These relationships can now be further investigated with this algorithm, which could potentially help adapt and optimize DO treatment protocols.

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