JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 8 (1997) 785–788

A biomechanical regulatory model for periprosthetic fibrous-tissue differentiation

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Loosening of implants in bone is commonly associated with a development of fibrous interface tissues, due to interface gaps and a lack of mechanical stability. It has been postulated that the differentiation of these tissues to fibrocartilage or bone is governed by mechanical stimuli. The objective of our research is to unravel these relationships to the extent that the question whether an implant will loosen can be answered from initial conditions determined by implant and interface morphology, and functional loads. In this project we studied the hypothesis that distortional strain and interstitial fluid flow are the mechanical stimuli governing tissue differentiation. For that purpose, a biomechanical regulatory model was developed and used in association with a finite element code to simulate animal experiments with implants moving in bone. The similarities between the implant incorporation process found in the experiment and its simulation with the computer model demonstrate that our hypothesis is viable from a regulatory point of view.

1. Introduction

A concern for effective applications of non-cemented joint replacement in orthopaedics is poor fit of the prosthetic components in bone. Gaps between implant and bone, in combination with the cyclic articular loads, promote relative motions. The lack of initial mechanical stability this creates may hamper bone ingrowth or osseus integration and even cause bone to resorb, and fibrous or fibro-cartilagenous tissue to be interposed at the implant–bone interface [1]. Eventually, early clinical loosening may result [2]. The problem addressed in this article is whether the probability of implant loosening as an effect of these phenomena could be predicted from implant and initial interface morphology, and functional loads.

Pauwels [3] postulated that tissue-differentiation processes starting from mesenchymal cell condensations to either fibrous tissue, fibrocartilage or bone, are governed by mechanical stimuli. Based on a finite-element analysis (FEA) of soft-tissue formation beneath a tibial-knee plateau, Giori *et al.* [4] concluded that the locations of fibrocartilage in interface tissue coincide with prominent hydrostatic stress. Similar relationships were reported for fibrous-tissue differentiation in fracture fixation [5]. Perren and Rahn [6] noticed that the morphology of fibrous encapsulation around bone screws tended to correlate with their motion patterns. We have confirmed this relationship and shown, in addition, that a similar correlation can be demonstrated for loosened hip- replacement components [7].

Søballe *et al.* [8] have demonstrated, using a force-actuated piston implant in canine bone, that periprosthetic tissue phenotype can be controlled by the extent of piston motion and the width of an initial gap. These experiments were analysed by Prendergast *et al.* [9, 10]. Using an FEA model of the experimental configuration, simulating dynamic force actuation and biphasic tissue properties, they demonstrated that biophysical stimuli on the cells in the tissue, such as strain, fluid pressure and interstitial fluid velocity, changed significantly while the interface tissue differentiated from loose granulative to fibrous connective and fibrocartilage, to bone. It was hypothesized [10] that these changes in mechanical tissue variables might actually regulate the differentiation in tissue

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Selected paper from the 13th European Conference on Biomaterials, Göteborg, Sweden.

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phenotype, instead of being just its effect, as suggested by Pauwels [3]. If this is true, then the differentiation time-trajectory of fibrous interfaces could possibly be controlled by prescription of mechanical variables, through manipulation of implant design and loading (Fig. 1). The objective of the present study was to investigate whether such an hypothesis is reasonable. For that purpose, FEA computer simulation of the piston micro-motion experiment [8] was performed, using a biomechanical regulatory feedback model to mimic the tissue differentiation time-trajectory.

2. Methods

The experimental device [8] is shown schematically in Fig. 2. An axisymmetric FE model was used as developed by Prendergast *et al.* [9, 10], representing the piston, the bony envelope and the gap in between. The piston was actuated by an intermittent force with an amplitude of 300 N, the maximal force available at the dog knee articulation in gait [11]. The saw-tooth loading profile is shown in Fig. 3.

The piston material was modelled as homogeneous, isotropic and linear elastic, with an elastic modulus of 2×10^5 MPa and a Poisson's ratio of 0.3. Bone and gap tissues were assumed biphasic with an inviscid fluid moving within a porous solid matrix [10, 12]. Using the DIANA FE-code (TNO, Delft, The Netherlands), strain and stress distributions in the matrix, fluid pressure and fluid velocity relative to the solid matrix could be calculated, depending on the piston load prescribed and the biphasic tissue properties allocated to the elements. Bone was given an elastic modulus of 4590 MPa and a fluid permeability of 3.7×10^{-13} m^4 N^{-1} s^{-1} [13]; the gap tissue properties were varied according to specifications predicted from the mechanical tissue variables. Appropriate boundary conditions were adjusted to the FE model for forces, displacements, pressures and fluid flow [10].

Initially, the gap tissue was assumed as uniform fibrous-connective, with an elastic modulus of 2.0 MPa and a permeability of 1.0×10^{-14} m^4 N^{-1} s^{-1}. The piston was incrementally actuated by the 300 N force profile and the mechanical tissue variables were calculated. Depending on the values of the maximal distortional strain, γ, and the relative fluid velocity, v, during a loading cycle, the elastic moduli and permeabilities in each element were updated after a full iteration. Based on measurements and literature data [8, 10] it was assumed, for that purpose, that (woven) bone, with a modulus of 4590 MPa and a permeability of 3.7×10^{-13} m^4 N^{-1} s^{-1} would emerge if

$$\gamma/a + v/b < 1 \tag{1}$$

where $a = 0.0375$ and $b = 3$ μm s^{-1}, as derived from the analyses of Prendergast *et al.* [10]; that tissue with a predominantly fibrocartilagenous phenotype, with a modulus of 10.0 MPa and a permeability of 5.0×10^{-15} m^4 N^{-1} s^{-1}, would develop if

$$\gamma/a + v/b > 1 \tag{2a}$$

and

$$\gamma/a + v/b < 3 \tag{2b}$$

and that fibrous connective tissue would be maintained if

$$\gamma/a + v/b > 3 \tag{3}$$

The regulation scheme applied in the iterative simulation study is illustrated in Fig. 4. Every iteration represents one loading cycle, as specified in Fig. 3. The amplitudes of the resulting tissue variables supposedly represent cell stimulation during an extended real-time period. The simulation process was continued until no more transitions in tissue type occurred. The hypothesis investigated can be considered acceptable

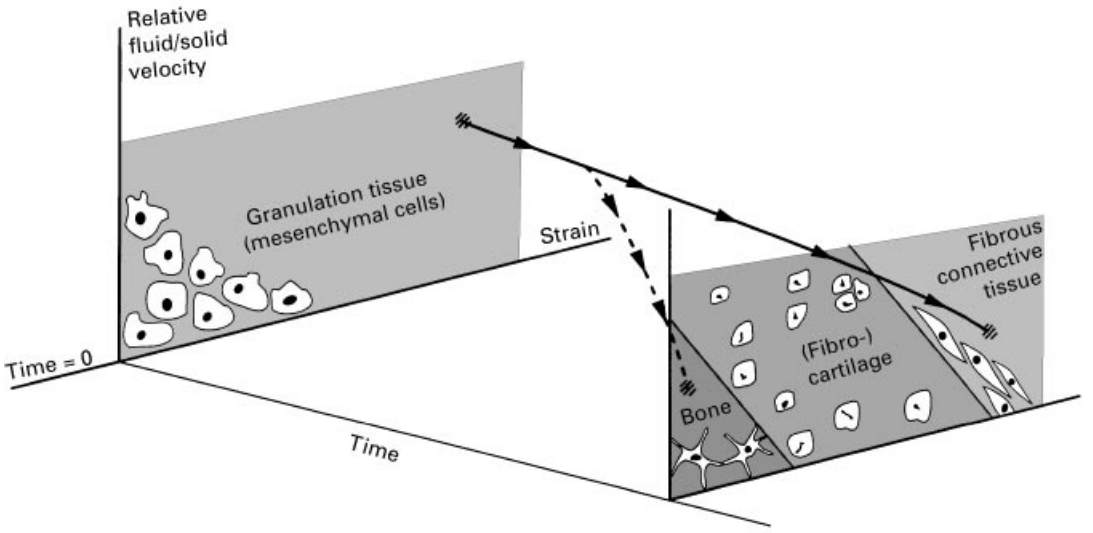

Figure 1 The hypothesis that fibrous-tissue differentiation is controlled by mechanical variables, such as distortional strain and interstitial fluid flow, implies that the time trajectory of tissue differentiation would depend on loading history. Depending on external loads and initial morphology, an implant interface may remain fibrous or turn to bone (reproduced from Prendergast *et al.* [10]; courtesy of Dr Marjolein van der Meulen, Cornell University, Ithaca, NY).

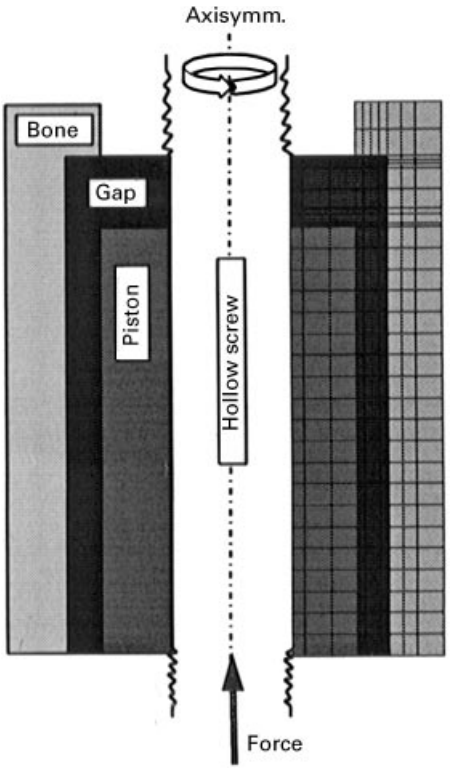

Figure 2 Axisymmetric FE model of the experimental configuration [8]. A gap of 750 μm is present between piston and bone.

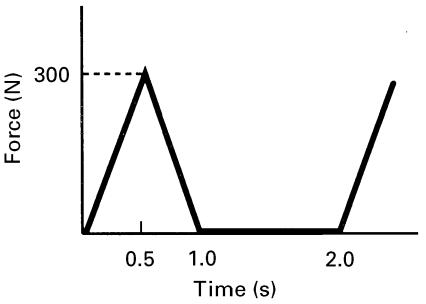

Figure 3 The cyclic force profile applied to the piston, assuming a 300 N maximal force available at the canine knee articulation [11].

if eventually all elements differentiate to ones representing bone, as eventually occurred in the experiments [8].

3. Results

At the first load application, the maximal piston displacement was 160 μm (Fig. 5); all the gap tissue was then still fibrous connective. The strain and fluid velocity amplitude distributions, developing due to the load, were non-homogeneous, in the sense that they differ depending on location in the tissue; hence, they differ per element. These values per element are illustrated in Fig. 6. When compared with the transition criteria above, it turned out that 1.5% had values favouring bone, 30.1% values favouring fibrocartilage, and 68.4% values favouring fibrous tissue (Fig. 6). These tissue transitions were then effected automatically in the model, by updating element moduli and

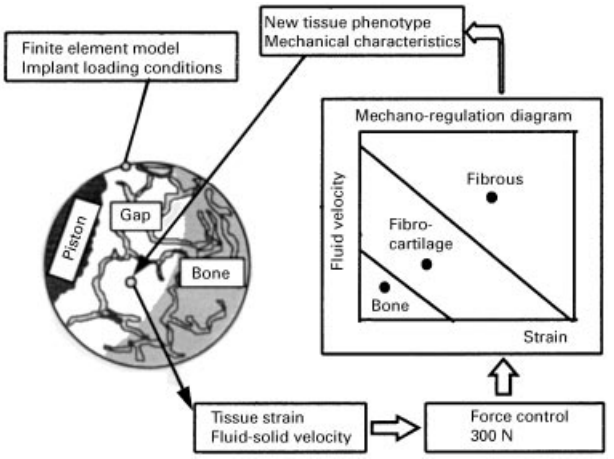

Figure 4 The regulatory scheme used in the computer simulation. The strain and fluid velocity distributions are calculated in the FE model. Based on the transition criteria, illustrated in a phase diagram, tissue-phenotype characteristics are updated. The simulation is continued until no more changes occur.

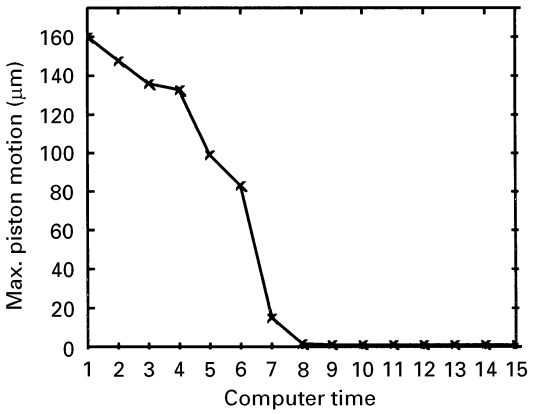

Figure 5 Development of the piston-displacement amplitude over (computer) time. Numbers on the horizontal axis signify iteration number.

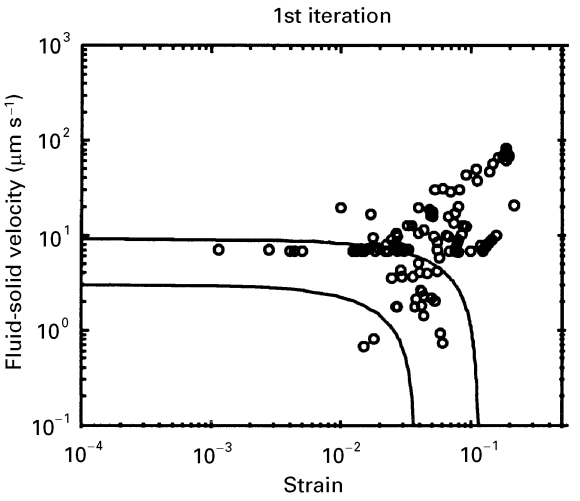

Figure 6 Phase diagram of tissue transition regions with element values of strain and fluid velocity after the first load application cycle (logarithmic scale).

permeabilities, before the next iteration was started. As an effect of these transitions, the tissue became stiffer, so that piston displacement had reduced to a 148 μm amplitude in the second iteration. Again, the

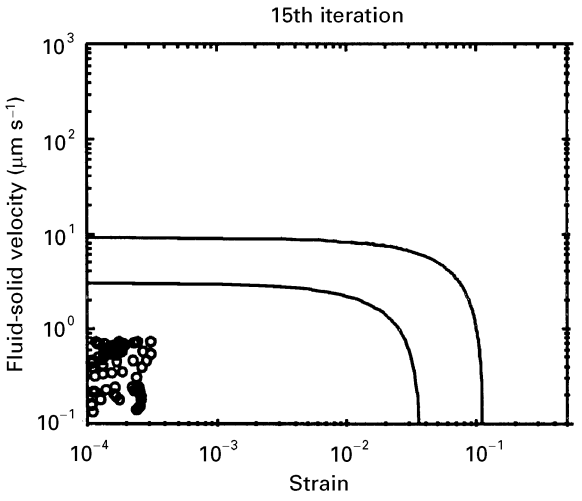

Figure 7 As Fig. 6, but after the final iteration. All elements have turned to bone.

strain and fluid velocity values were considered and updated relative to the transition criteria, before a new iteration was started. In this process, piston displacement gradually reduced, due to progressive stiffening of the tissue (Fig. 5). Eventually, all elements turned to bone, most of them through fibrocartilage as an intermediate stage (Fig. 7).

4. Discussion

The results obtained demonstrate that the experimental findings of Søballe *et al.* [8] are compatible with the paradigm of Pauwels [3], according to which mechanical stimuli would govern tissue differentiation. In the animal experiments, the gap tissue gradually differentiated from granulative to fibrous connective, to fibrocartilage and finally to bone. Prendergast *et al.* [10] showed that this transition was accompanied by a cascade of mechanical phenomena. The tissue transitions increase its stiffness and reduce its fluid permeability, thus increasing its resistance against deformation. As a result, motion-controlled piston actuation gives way to a load-controlled mode, because the maximal available gait force of 300 N can no longer cause the piston to bottom out [10]. While the tissue differentiates further it becomes stiffer still, reducing piston motion, tissue strains and fluid velocities even more. What we have shown here is that if we assume tissue strain and fluid velocity to be causative stimuli to differentiation, and materialize this assumption in a computer simulation model, the predictions of tissue differentiation sequences coincide with those found experimentally.

That our results are consistent with the hypothesis investigated does not prove that it is true. Although interface soft-tissue development is known to be related to mechanics [1, 6, 7], and cells are metabolically stimulated by both strains [14] and fluid flow [15], the biological factors tying mechanical stimuli to cell differentiation are not known. We assume that the cell types involved proliferate in a window of mechanical extra-cellular matrix (ECM) conditions, characterized by distortional strain and fluid flow, the threshold values of which differ depending on cell type. Although hydrostatic stress was suggested to be a prominent governing mechanical stimulus [5], based on linear elastic analyses of fibrous tissues, our earlier biphasic analysis of the canine experiments could not confirm that [9]. However, we have not attempted to apply it in a similar analysis, as described here. Evidently, high local gradients in fluid pressure cause fluid flow, so these two variables are not independent.

Further experimentation is required before the regulatory model proposed here can be applied for practical purposes, as for instance in design or preclinical testing of implants. In concept, the present model is similar to those applied to predict strain-adaptive bone remodelling around implants [16]. But where those were validated for practical applications, the present soft-tissue differentiation model has only a preliminary status. Nevertheless, the results presented here demonstrate the concept of distortional tissue strain and relative fluid velocity as mechanical variables controlling peri-prosthetic tissue phenotype to be viable. This encourages further investigations of its predictive capacities.

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Received 5 May
and accepted 12 May 1997