

Finite element analysis of fibrous tissue morphogenesis : a study of the osteogenic index using a biphasic approach

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**FINITE ELEMENT ANALYSIS OF FIBROUS TISSUE
MORPHOGENESIS — A STUDY OF THE OSTEOGENIC INDEX
USING A BIPHASIC APPROACH¹**

П. Прендергаст, Р. Хьюскес

**КОНЕЧНО-ЭЛЕМЕНТНЫЙ АНАЛИЗ МОРФОГЕНЕЗА ВОЛОКНИСТОЙ
ТКАНИ — ИЗУЧЕНИЕ ОСТЕОГЕНИЧЕСКОГО ИНДЕКСА В ДВУХФАЗНОМ
ПОДХОДЕ¹**

An axisymmetric finite element model of the soft gap tissue and surrounding cancellous bone was developed to analyse the biomechanical behaviour of the environment surrounding the implant. Both isotropic linear and biphasic representations of constitutive behaviour for the tissues were considered. The biphasic approach models the tissue as a control system of a solid and a fluid "perfusant". The work presented assumes a technological significance for rational design of load bearing implants.

Осесимметричная конечно-элементная модель мягкой ткани и окружающей пористой кости разработана для анализа биомеханического поведения среды, окружающей имплантант. Рассмотрены два представления механического поведения тканей: изотропное линейно-упругое и двухфазное. При двухфазном подходе ткань моделируется как система, состоящая из твердого и жидкого компонентов. Работа имеет технологическое значение для рационального проектирования нагруженных имплантантов.

The development of tissues in the skeleton is a complex process beginning with a mesenchymal cell condensation and finishing with some 'equilibrium' tissue suited to the mechanical function required for the particular skeletal part. The process involves differentiation of the pluripotent mesenchymal cells into those that form the particular equilibrium tissue, e.g. chondrocytes for cartilage or osteoblasts for bone. Several philosophers in the previous century have hypothesised that the process is not just genomic, but that mechanical factors play a part in determining the pathway which is followed [1]. Nonetheless, very little is yet known about the mechanical events that underlie the tissue formation process.

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Based on an idea proposed by the German orthopaedic surgeon F. Pauwels [2] concerning the relative influence of hydrostatic and shear stresses, it has been proposed by Carter [3] that the tendency for fibrous connective tissue or cartilage ossification could be captured by an osteogenic index

$$OI = \sum_{i=1}^c n_i (S_i + kD_i) \quad (1)$$

where S and D denote the cyclic octahedral shear stress and hydrostatic stress respectively, k is a constant weight factor, n_i is the number of loading cycles of a particular loading condition and c is the number of such different loading conditions. Representing the tissue as an elastic and isotropic solid, finite element models have been developed to analyse the morphogenetic behaviour of tissues [3–5]. It has been suggested that this kind of modelling approach is able to describe features of fracture repair and chondrogenesis [3], and ligament [4] and tendon [5] tissue phenotype.

Despite the convenience of the elastic approach, it is clear that the tissue itself is a material containing both solid and fluid constituents (called a biphasic material). The solid phase is mainly a certain type of collagen mixed with proteoglycans, whereas the fluid phase consists of blood and interstitial fluid. Since the cells that undergo differentiation (mesenchymal cells) are contained in the fluid until they become precursors for tissue forming cells [6], it seems worthwhile to ask whether or not a model derived from the fundamental biphasic nature of the tissue would lead us towards a better understanding of the phenomenon of tissue development.

To investigate this idea, we generated a finite element model of peri-prosthetic tissue formation observed in an animal experiment, using both elastic and biphasic [7] finite element analyses. The animal experiments analysed in this investigation have been reported in the doctoral thesis of Sjøballe [8]. The osteogenic index was calculated in the gap between implant and bone, using both linear elastic and biphasic tissue models. Since the fluid phase moves relative to the solid, it is possible that the osteogenic stimulus might arise as a result of fluid motion. To investigate this, the velocity of fluid relative to solid phase was calculated. Results are compared to the histological results reported by Sjøballe [8]. Finally, some discussion of how a biophysical morphogenic stimulus might really arise is given.

Methods

Sjøballe [8] implanted a micromotion device into the condyles of dogs (Fig. 1). The implant was attached to a piston that moved axially under the load of weight bearing. Axial movement was limited to either 150 μm in one set of experiments and 500 μm in another. The spring ensured that the implant returned to the lower position when the weight-bearing load was removed. The effects of these levels of micromotion were compared with those in animals where all motion of the implant was restrained. The effect of different implant coatings was also investigated but that effect will not be considered in this paper. A gap of 750 μm was retained around the

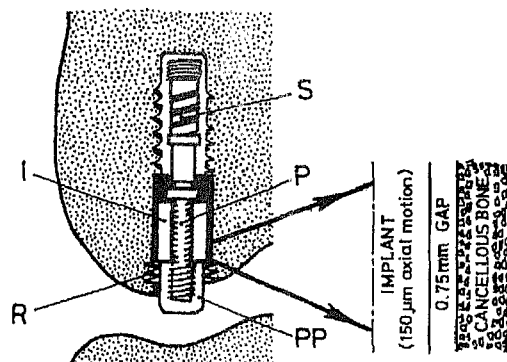


Fig. 1. From Søballe [8], the micromotion device with implant (*I*) screwed onto piston (*P*). The spring (*S*) is contained in a hollow screw. A polyethylene plug (*PP*) extends below the bone surface to engage the lower condyle on loading.

Рис. 1. Устройство микродвижения с имплантатом (*I*), ввинченным в поршень (*P*) [8]. Пружина (*S*) находится в пустотелом винте. Полиэтиленовая заглушка (*PP*) надевается под костной поверхностью для зацепления с нижним мыщелком при нагружении.

implant within which tissue formed. Depending on the extent of the micromotion and the time after implantation, various amounts of fibrous connective tissue, fibrocartilage or bone were formed in the peri-implant gap.

An axisymmetric finite element model of the gap tissue and surrounding cancellous bone was developed to analyse the biomechanical behaviour of the environment surrounding the implant. Two kinds of constitutive behaviour for the tissues were considered:

- an isotropic linear elastic representation, where the Young's modulus and Poisson's ratio were approximated by 1 MPa and 0.1667 for soft gap tissue and 100 MPa and 0.3 for cancellous bone;
- a biphasic representation, where gap tissue and cancellous bone were considered to contain fluid. The permeability of the cancellous bone was taken to be $3.71 \cdot 10^{-15} \text{ m}^4/(\text{N} \cdot \text{s})$ [9]. The permeability of the gap tissue has not been measured. Armstrong and Mow [10] determined the permeability of cartilage as a function of water content. According to their results, $2.0 \cdot 10^{-15} \text{ m}^4/(\text{N} \cdot \text{s})$ is approximately a permeability corresponding to an equilibrium modulus of 1 MPa.

The displacements in the model were restrained at the cancellous border, and prescribed to move 150 μm at the implant/gap interface (Fig. 2). For the biphasic model, a nonlinear finite element solution was obtained with a time step of 0.02 s using 25 iterations to reach the maximum deflection of 150 μm , and the same to return to the zero displacement position; thereafter 1 s of no loading was simulated using a 0.1 s time step. For the biphasic model, considerable variation in the solution occurs depending on the pressure and velocity prescriptions at the boundary. In the eventual analysis, the fluid velocity was set to zero at the boundary of the cancellous bone in the model, and the pressure was prescribed to be zero at the distal end.

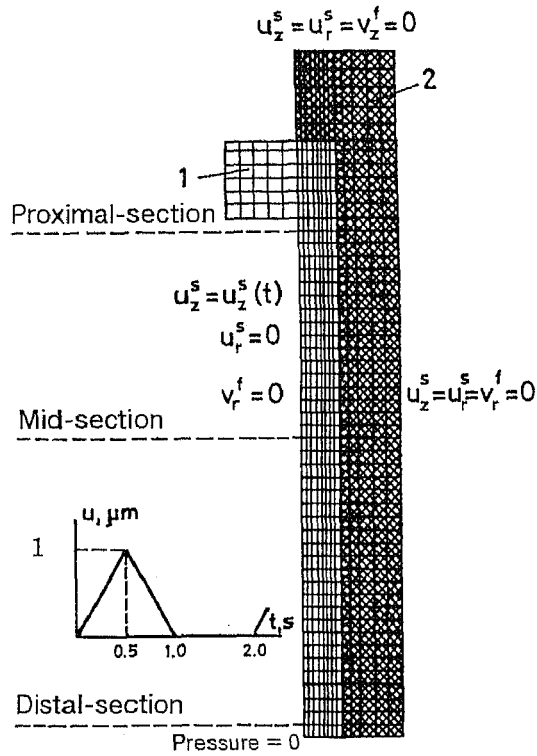


Fig. 2. Finite element model of the gap tissue and bone tissue with restraints indicated for the biphasic tissue representation. The inset shows the loading mode. The labels "proximal", "middle" and "distal" refer to the positions where the osteogenic index is reported.

Рис. 2. Конечно-элементная модель мягкой (1) и костной (2) тканей при ограничениях на перемещения, принятых в двухфазном представлении ткани. Графическая вставка показывает режим нагружения. Метки "близкий", "средний", "удаленный" указывают расчетные сечения для остеогенического индекса.

Since the tissue in the peri-implant gap is undergoing tissue differentiation, there is an interchange of mass between the fluid phase and the solid phase (the solid phase consists of collagenous constituents and, for bone, hydroxyapatite constituents). In this case the balance laws for a biphasic mixture (see [7]) have to include terms relating to the reactive nature of the mixture [11]. For the mixture as a whole, the balance equations for the mass requires,

$$c^s + c^f = 0 \quad (2)$$

where c denotes the rate of mass transfer per unit volume [$\text{kg} \cdot \text{s}^{-1}/\text{m}^3$] and the superscripts denote solid and fluid, respectively. In addition to the Stokes drag (denoted π), the balance of linear momentum must include "reactivity" terms, i.e.

$$\pi^s + \pi^f + \rho^s c^s \mathbf{v}^s + \rho^f c^f \mathbf{v}^f = 0 \quad (3)$$

where ρ denotes density and \mathbf{v} denotes the velocity. For a homogeneous medium,

$$\pi^f = -\pi^s = K (\mathbf{v}^s - \mathbf{v}^f)$$

where K is the diffusive drag coefficient related to the permeability (denoted k), as $k = \phi_f^2/K$, where ϕ_f is the volume fraction of fluid [12]. The terms in equation (3) have units of momentum per unit volume per unit time. Finally, the first law of thermodynamics gives

$$r^s + r^f + c^s \left(\varepsilon^s + \frac{1}{2} \mathbf{v}^s \cdot \mathbf{v}^s \right) + c^f \left(\varepsilon^f + \frac{1}{2} \mathbf{v}^f \cdot \mathbf{v}^f \right) + \pi^s \cdot \mathbf{v}^s + \pi^f \cdot \mathbf{v}^f = 0 \quad (4)$$

where r denotes the heat production of the constituents and ε denotes the specific internal energy. Note that the bracketed terms of equation (4) contain both the internal energy and the kinetic energy of the transferred mass, and therefore assume that the new mass is energetically indistinguishable from the mass already present at that position in that phase.

The second law of thermodynamics for a reacting continuum has been considered by Truesdell [13] and by Kelly [11]. Entropy flows between constituents are postulated to account for the self-organisational events in the tissue [14]. Despite the evident importance of this hypothesis, it will not be discussed in this paper.

Results

The osteogenic index [defined in equation (1) above] was calculated in the gap tissue for both linear elastic and biphasic material descriptions. For the biphasic material description it refers to the relationship between the deviatoric and hydrostatic stresses in the solid phase only, so it is not an apparent level quantity. Considering the linear elastic representation, the osteogenic index was found to decrease across the gap (Fig. 3), and the decrease was linear at the mid-section of the implant. The values calculated in this study are numerically similar to those found by Carter [3] for a fracture callus. With the biphasic representation, the variation was completely different because the solid tissue was deformed substantially by the drag forces generated by fluid flow. Specifically, fluid flow occurs opposite to the direction of implant motion, due to the pumping action of the implant. The result is tissue deformation opposite to the direction of implant motion, and exudation of fluid from the distal end of the gap.

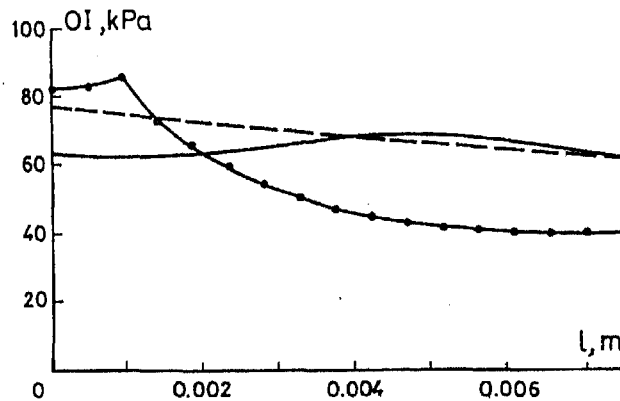


Fig. 3. Linear elastic tissue model: Osteogenic index in the gap tissue and a graph of osteogenic index as a function of radial distance from the implant surface, for the proximal (—●—), middle (— — —), and distal (—) gap sections.

Рис. 3. Линейно-упругая модель: зависимость остеогенического индекса OI мягкой ткани от радиального расстояния от поверхности имплантата l для ближнего (—●—), среднего (— — —) и удаленного (—) сечений.

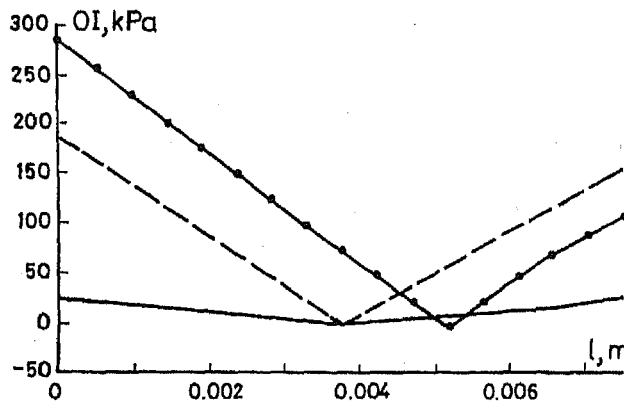


Fig. 4. Biphasic tissue model: Osteogenic index in the gap tissue and a graph of osteogenic index as a function of radial distance, 0.5 (---●---); 1.0 (---); 1.5 s (—) in the loading cycle (mid-section only reported).

Рис. 4. Двухфазная модель ткани: зависимость остеогенического индекса OI мягкой ткани от радиального расстояния от поверхности имплантата l в следующие моменты цикла нагружения: 0,5 (---●---), 1,0 (---) и 1,5 с (—) (относится только к среднему сечению).

Therefore, whilst the tissue attached to the implant moved the full 150 μm , the tissue further into the gap was forced (due to fluid drag) to displace in the opposite direction. This explains the different osteogenic index values calculated for the biphasic tissue representation. Furthermore, due to the nonlinear nature of the biphasic effect, the osteogenic index varied during the load cycle (Fig. 4).

The velocity of the fluid was calculated to ascertain whether or not the momentum transfer due to the change in velocity is largely relative to the momentum transfer due to the change in mass. The velocity of the fluid relative to the solid in the axial direction reaches a maximum value of approximately $1.25 \mu\text{ms}^{-1}$ (Fig. 5). Therefore, an estimate of the momentum supply to the fluid phase is given by

$$\pi^f = K (v^f - v^s) \approx \frac{1}{2.0 \cdot 10^{-15}} \cdot 1.25 \cdot 10^{-6} \approx 6.25 \cdot 10^8 \text{ kg} \cdot \text{m}^{-2} \cdot \text{s}^{-2}.$$

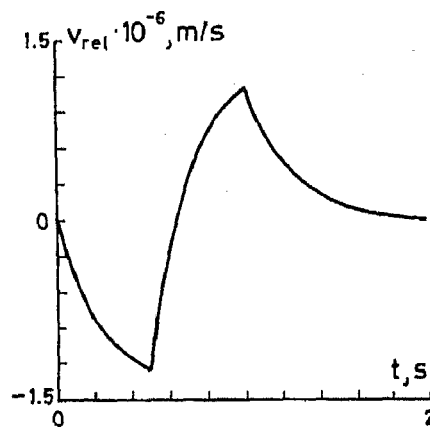


Fig. 5. Fluid velocity vs. time, for a sampling position midway down the implant and halfway across the gap.

Рис. 5. Зависимость относительной скорости жидкости v_{rel} от времени t при тестировании на полудлине к имплантату и поперечному зазору.

An estimate of the momentum supply to the mixture due to reactivities [i.e. the third and fourth components of equation (3)] can be obtained by considering that, in this particular experiment, fibrous encapsulation by fibrous connective tissue was observed after four weeks (i.e. approximately $2.4 \cdot 10^6$ s) when the implant was under no micromotion. Assuming a linear rate of mass formation and approximating the density as $1000 \text{ kg} \cdot \text{m}^{-3}$, and, from equation (2) $c = c^s = -c^f$, we can approximate the sum of the reactivity terms as

$$\rho c (\mathbf{v}^s - \mathbf{v}^f) \approx 1000 / (2.4 \cdot 10^6) \cdot 1.25 \cdot 10^{-9} \approx 5.2 \cdot 10^{-10} \text{ kg} \cdot \text{m}^{-2} \cdot \text{s}^{-2}.$$

In this way, it is shown that the terms due to reactivity are much smaller than those due to mechanical momentum transfer (Stokes drag) and can therefore, as a first approximation, be neglected in this analysis. We return to this important point in the discussion.

Discussion

Before discussing the results, we must acknowledge that any mathematical model of morphogenesis must be riddled with simplifications because of the extreme complexity of the morphogenetic process. The benefits of a biphasic material approach over an elastic material approach might seem obvious at first since the tissue contains both collagenous solids and blood as well as water fluids. However, the elastic osteogenic index [3] and the accompanying arguments about cell shape [5, 15] have allowed quantification of the role of mechanical factors in morphogenesis and skeletal regeneration. The present results additionally show that the osteogenic index might not be linked in any direct way to the forces acting on mesenchymal cells, or any precursor cells, that are transported in the fluid. Even for cells lodged in the solid phase of the fibrous tissue, such as chondrocytes or fibrocytes [16], the flow of the fluid can significantly alter the deformation of the solid due to Stokes drag forces — though this result must be taken tentatively given that the permeability of the peri-implant fibrous tissue has not yet been measured. Recent work has shown that this conclusion could hold true in other biomechanical systems [17].

To what extent does the biphasic finite element model developed in this paper represent the actual structural behaviour of the implant/gap/cancellous bone system? The geometry is well defined, but the boundary conditions and material properties can only be approximated at this stage. We have assumed that no fluid flow occurs into the volume under analysis, i.e. that sufficiently far into the cancellous bone, there is no effect of the implant. This assumption seems to be a good one if the cancellous bone is clogged with marrow at some distance away from the cancellous bone/fibrous tissue junction. However, if the gap tissue vascularises, the system will no longer be closed with respect to mass. Angiogenesis may occur, and arteries and veins will traverse this boundary creating fluid flows into the system. Regarding material properties, the gap tissue has been analysed histologically, and found to be either fibrous connective tissue or fibrocartilage or a mixture of the two [8]. The permeability of this tissue has not been

measured, however, and this is a serious limitation to the present analysis. For the moment, we rely on the values measured for cartilage as a function of Young's modulus and water content [10].

The different osteogenic index in the biphasic material model arises because the deformation of the tissue is not linear across the gap. The result is that the maximum shear strains occur near the implant surface and the bone surface causing the osteogenic index to be large there, and to have a minimum near the centre of the gap. It is noteworthy that tissue development begins on these surfaces in reality (see Søballe [8]). On the other hand, the elastic material model obviously predicts constant decrease in shear across the gap resulting in a similar constant variation of the osteogenic index. Thus, the osteogenic index prediction seems to work best when the tissue is modelled as a biphasic material.

The biphasic approach to tissue modelling presented in this paper is analogous to the bone remodelling approach which models the tissue as a control system of a solid and a fluid 'perfusant' (Cowin and Hegedus [18]). In bone remodelling, it is assumed that the forces of interaction between the components of the tissue are small compared with the forces in the solid component. The tissue morphogenesis analysis presented in this paper differs from the bone remodelling analysis since, for example, the fluid/solid interaction has a significant importance and is accounted for; and the whole system is considered closed with respect to mass — i.e. any new collagenous tissue generated must come from the materials present in the fluid and precursor tissues whereas the mass balance of adaptive elasticity theory [18] does not account for the 'perfusant'. No momentum of energy crosses the boundary except the one introduced mechanically due to the motion of the implant. Since the time required for fibrous encapsulation of the peri-implant gap was determined experimentally, we have been able to approximate the fluid-to-solid mass exchange rate and thus calculate values for the last two terms of equation (3). It is seen that, when the rate of tissue formation is assumed linear, the momentum transfer due to reactivity is negligible. Some further discussion is needed on this point because, in truth, the tissue formation rate is unlikely to be linear. Instead, morphogenesis most likely proceeds as a series of "bursts" or "local explosions" where the mass transfer rate between phases is, for some brief period of time, very high. If this were to be true, then the reactivity terms of equation (3) might be important determinants of the partial stresses of the solid and fluid phases. It is possible that these 'explosions' might originate from mechanical energy released from microdamage of the collagenous network. This could initiate a remodelling response in a process of attuning the tissue to its mechanical environment [19].

The work presented here assumes a technological significance for the design of load bearing implants. Very complex stress patterns occur at the junctions between implant and bone, and these complex stresses are responsible for a host of failure interactions [20]. In particular, fibrous tissue formation occurs on the bone/implant interface of intramedullary fixated implants. The rational design of these load bearing structures will eventu-

ally require a method for analysis and prediction of fibrous tissue formation. The present approach is offered as a promising basis for such analysis.

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