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Cellular poroelasticity: A theoretical model for soft tissue mechanics

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ABSTRACT: This paper presents a theoretical model for the mechanics of soft biological tissues. It is based on the hypothesis that tissue can be regarded as a recursively poroelastic material, composed of a poroelastic extracellular matrix in which poroelastic cells are embedded. A set of equations describing such "cellular poroelastic" material are presented, and subsequently used to study the consolidation of a one-dimensional sample of tissue. The model predicts a difference between the intra and extra-cellular fluid pressures, which depends on the consolidation coefficients and characteristic length scales of cells and tissue. This behaviour is reminiscent of the "secondary consolidation" phenomenon sometimes observed in geomechanics. Experiments are required to further explore this theoretical model.

1. INTRODUCTION

Several models have been proposed to investigate the biomechanics of soft biological tissues based on Biot's poroelastic theory. They include, among others, successful applications in the study of arterial walls (Simon et al. 1993), skin (Mak et al. 1994), cardiac muscle (Yang and Taber 1991), and articular cartilage (Mow et al. 1986).

All these models have been based on the conception of tissues as structurally bi-phasic, i.e. composed of a solid matrix saturated by interstitial fluid. However, the main characteristic of tissues is that they are made up of cells: each one of them a complex organism in itself, both biologically and structurally (Alberts 1989). A sensible refinement for the classical poroelastic model, as applied in biomechanics, would then be to include the existence of the cells as differentiated structures within tissues. Such 'cellular poroelastic' model would be relevant, for example, for situations in which it is of interest to know the regional intra-cellular and extra-cellular water contents of tissue, e.g. in the case of cytotoxic or vasogenic oedema.

The objective of this study has been to modify the classical poroelastic paradigm, in order to take into account explicitly the effect of the micro-mechanics of cells on the macro-mechanics of tissue. This has been done based on the following hypothesis: soft biological tissue can be regarded as a recursively poroelastic material, composed of a poroelastic extracellular matrix in which poroelastic cells are embedded (Peña 1996).

In the following sections we will present: a brief description of soft tissues, the biomechanical model proposed and its application to the study of the consolidation of a one-dimensional sample of tissue.

2. SOFT BIOLOGICAL TISSUES

Tissues are the aggregation of cells, but they are not made exclusively of cells. A substantial part of their volume is extra-cellular space, which is largely filled by an intrincate network of macromolecules called extracellular matrix. One of the functions of this matrix is to hold cells and tissues together.

2.1 *Cells*

A typical animal cell is composed of a nucleus, a cytoskeleton, a series of organelles and a plasma membrane. The organelles ('small organs') occupy approximately half of the intra-cellular volume. The cytoskeleton is a complex network of filaments that criss-cross the cell in all directions. There is increasing evidence that a major function of some of these filaments is to resist mechanical stress (Alberts et al. 1989). The cell membrane is composed of lipid and protein molecules. Some of these proteins form channels which allow the transport of ions and other substances across the cell membrane.

2.2 *Extracellular matrix*

There are many different kinds of tissues in the human body. Despite their differences, however, they can be theoretically classified somewhere in the spectrum between connective and epithelial tissues, depending on the structural roles played by the extracellular matrix and the cells.

Connective tissue is mostly made up of matrix and the cells are sparsely distributed within it. "The matrix is rich in polymers (especially collagen) and it is the matrix -rather than the cells- that bears most of the mechanical stress to which tissue is subjected" (Alberts et al. 1989: 949). The cells are attached to components of the matrix but direct attachments between cells are relatively unimportant.

Epithelial tissue, in contrast, is mostly made up of cells and the matrix is scarce. "Here the cells themselves, rather than the matrix, bear most of the mechanical stress by means of strong intracellular protein filaments (components of the cytoskeleton) that criss-cross the cytoplasm of each cell" (Alberts et al. 1989: 950). In order to transmit mechanical stress from one cell to the next, the filaments are directly or indireclty attached to transmembrane proteins in the plasma membrane.

3. CELLULAR POROELASTICITY

3.1 *Physical model*

Based on the preceding general description of tissues, the following hypothesis is proposed: soft biological tissue can be regarded as a recursively poroelastic material, composed of a poroelastic extracellular matrix in which poroelastic cells are embedded. The mechanical behaviour of the whole tissue, thus, is dictated by the interaction of the generalised (extracellular) macroscopic consolidation process and the localised (intra-cellular) macroscopic consolidation process. These micro and macro consolidations are linked by the exchange of fluid between the intracellular and extracellular spaces, and by the continuity of stresses across the boundary between them, i.e. the plasma membrane of cells.

Then, in the framework of this hypothesis, for tissue, the corresponding solid matrix will be the extracellular matrix and the fluid the extracellular fluid; and for cells, the solid matrix will be the cytoskeleton and organelles and the fluid the intracellular fluid. During consolidation, the path of the drainage of the fluid will be from the intracellular space into the extracellular space via the plasma membrane, and then out of the tissue via the boundaries of the sample.

The relative effects of the micro and macro consolidations could then be computed from a weighted average, based on the ratio of the volumes of the intra and extra-cellular spaces to the total volume of tissue, i.e. their volume fractions. This will make the model flexible to accommodate the behaviour of different kinds of tissues, *e.g.* epithelial and connective.

In consequence, the present model is limited to the 'mechanical' behaviour of tissue, i.e. without taking into account the cellular ionic potentials of Na, K and Ca.

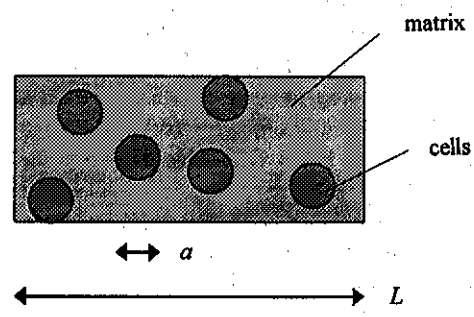

Figure 1. Idealisation of a cellular poroelastic material (not to scale).

3.2 *Mathematical model*

Implementing the complete cellular poroelastic idealisation, will require to solve $n+1$ consolidation problems: one macroscopic (for the matrix) and n microscopic (for the cells). In order to avoid this, it is proposed that two independent coordinate systems (x and ξ) are used for the macroscopic and microscopic domains. These domains will be denoted by Ω and Ω^l, with boundaries Γ and Γ^l, for the matrix and cells respectively. Thus, any point in the tissue could be represented as a point in a higher-dimensional space (x,ξ,t).

For the cells we have

$$\mu^{(i)}\frac{\partial^2 u^{(i)}_i}{\partial \xi_j \partial \xi_j}+\left(\mu^{(i)}+\lambda^{(i)}\right)\frac{\partial e^{(i)}}{\partial \xi_i}-\frac{\partial p^{(i)}}{\partial \xi_i}=0$$

$$K^{(i)}_{ij}\frac{\partial^2 p^{(i)}}{\partial \xi_j \partial \xi_j}-\frac{\partial e^{(i)}}{\partial t}=Q^{(i)} \qquad (1)$$

For the extra-cellular matrix we have

$$\mu^{(e)}\frac{\partial^2 u^{(e)}_i}{\partial x_j \partial x_j}+\left(\mu^{(e)}+\lambda^{(e)}\right)\frac{\partial e^{(e)}}{\partial x_i}-\frac{\partial p^{(e)}}{\partial x_i}=0$$

$$K^{(e)}_{ij}\frac{\partial^2 p^{(e)}}{\partial x_j \partial x_j}-\frac{\partial e^{(e)}}{\partial t}=Q^{(e)} \qquad (2)$$

where the superscripts *(i)* and *(e)* represent intracellular and extracellular, respectively; and the other indexes and variables have their usual meanings.

As we mentioned before, the connection between the micro and macro consolidations is by means of 1. the identity of stresses, *i.e.* $p^{(i)}(\Gamma^l,t) = p^{(e)}(\Gamma^l,t)$, and 2. the continuity of flows, *i.e.* $Q^{(i)} = -Q^{(e)}$, across the plasma membranes of cells.

4. EXAMPLE: 1D CONSOLIDATION

4.1 *Field equations*

In order to investigate this model, let's consider a simple one-dimensional case. A sample of tissue of length L, free drained at its boundaries, is subject to a load σ at $t = 0$. It will be assumed that the concentration of cells is small, thus $Q = 0$.

According to equation (1) the extracellular fluid pressure, thus, must satisfy

$$K^{(e)}(2\mu^{(e)}+\lambda^{(e)})\frac{\partial^2 p^{(e)}}{\partial x^2}=\frac{\partial p^{(e)}}{\partial t} \qquad (3)$$

$$p^{(e)}(0,t)=p^{(e)}(L,t)=0$$

$$p^{(e)}(x,0)=\sigma$$

While, for a cell located at point x, the intracellular fluid pressure must satisfy

$$K^{(i)}(2\mu^{(i)}+\lambda^{(i)})\frac{\partial^2 p^{(i)}}{\partial \xi^2}=\frac{\partial p^{(i)}}{\partial t} \qquad (4)$$

$$p^{(i)}(x,0,t)=p^{(i)}(x,a,t)=p^{(e)}(x,t)$$

$$p^{(i)}(x,\xi,0)=\sigma$$

where a represents the diameter of a typical cell.

4.2 *Analytic solutions*

Equation (3) is a classical consolidation problem which was solved by Terzaghi (1948) giving

$$p^{(e)}(x,t)=\sum_{n=1}^{\infty}\frac{2\sigma}{n\pi}\left(1-\cos n\pi\right)\sin\left(\frac{n\pi}{L}\right)e^{-\lambda_n \alpha t}$$

Equation (4) is a non-homogeneous initial-boundary value problem with parameter x. This problem can be solved using classical Fourier series methods (Strauss 1992) resulting in

$$p^{(i)}(x,\xi,t)=\sum_{m=1}^{\infty}p_m^{(i)}(x,t)\sin\left(\frac{m\pi\xi}{a}\right)$$

where

$$p_m^{(i)}(x,t)=\frac{2\sigma}{m\pi}(1-\cos m\pi)e^{-\lambda_m \beta t}$$

$$+\frac{2m\pi\beta}{a^2}(1-\cos m\pi)\times$$

$$\sum_{m=1}^{\infty}\frac{2\sigma}{m\pi}(1-\cos m\pi)\sin\left(\frac{n\pi x}{L}\right)\frac{e^{-\lambda_n\alpha t}-e^{-\lambda_m\beta t}}{\lambda_m\beta-\lambda_n\alpha}$$

As we are not actually interested in the detailed intra-cellular pressure distribution but on its average, we can integrate $p^{(i)}$ over each cell (thus eliminating coordinate ξ).

After some algebra and by making these equations non-dimensional, we obtain:

$$R^{(e)}(x,t)=\frac{2}{\pi\sigma}\sum_{n=1}^{\infty}\left(\frac{T_n}{n}\right)\sin\left(\frac{n\pi x}{L}\right)e^{-\frac{n\pi^2 t}{T_\alpha}} \qquad (5)$$

and

$$R^{(i)}(x,t)=\frac{2}{\pi\sigma}(A+B) \qquad (6)$$

where

$$A=\sum_{m=1}^{\infty}\frac{1}{\pi}\left(\frac{T_m}{m}\right)^2 e^{\frac{-m^2\pi^2 t}{T_\alpha}}$$

$$B=\sum_{n=1}^{\infty}\sum_{m=1}^{\infty}\frac{1}{\pi}\frac{T_n T_m^2}{n}\sin\left(\sqrt{\lambda_n}x\right)\frac{e^{\frac{-n^2\pi^2 t}{T_\alpha}}-e^{\frac{-m^2\pi^2 t}{T_\beta}}}{\left(m^2-n^2\frac{T_\alpha}{T_\alpha}\right)}$$

where the paramaters used are defined as

$$T_\alpha=\frac{L^2}{\alpha} \qquad \alpha=K^{(e)}\left(2\mu^{(e)}+\lambda^{(e)}\right)$$

$$T_\alpha=\frac{a^2}{\beta} \qquad \beta=K^{(i)}\left(2\mu^{(i)}+\lambda^{(i)}\right)$$

$$T_n=1-\cos n\pi \qquad \lambda_n=\left(\frac{n\pi}{L}\right)$$

$$T_m=1-\cos m\pi \qquad \lambda_m=\left(\frac{m\pi}{a}\right)$$

5. RESULTS

This simple one-dimensional consolidation problem, then, is fully defined by either of the parameter vectors:

$$(\alpha,\beta,a,L) \text{ or } (\alpha,\beta,T_\alpha,T_\beta)$$

in which a is the cell size, L the size of the sample, α and β consolidation coefficients, and T_α and T_β can be interpreted as draning coefficients.

Using equations (5) and (6) we can graph the behaviour of a sample of tissue with L=1cm and a=10 μm (a typical diameter for an animal cell). In the following two figures we can observe the distributions of $R^{(e)}$ and $R^{(i)}$ as functions of x and t.

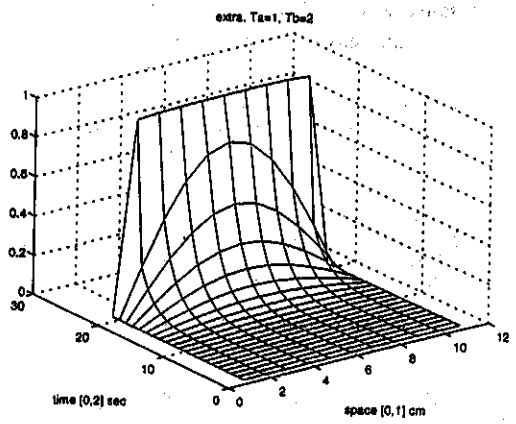

Figure 2. Extracellular pressure $R^{(e)}(x,t)$ for T_a = 1 and T_b = 2.

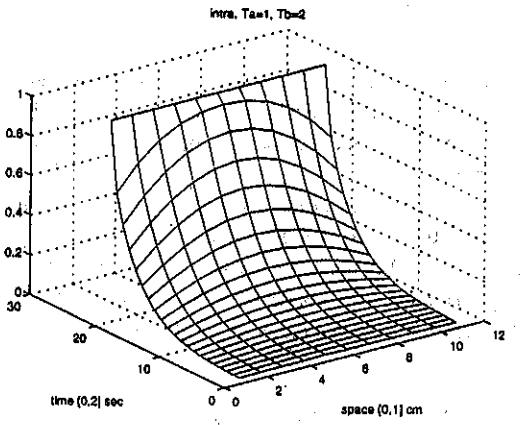

Figure 3. Intracellular pressure $R^{(i)}(x,t)$ for T_a = 1 and T_b = 2.

Using again equations (5) and (6) we can graph the evolution of the fluid pressures at the midpoint of the sample, for different values of T_α and T_β.

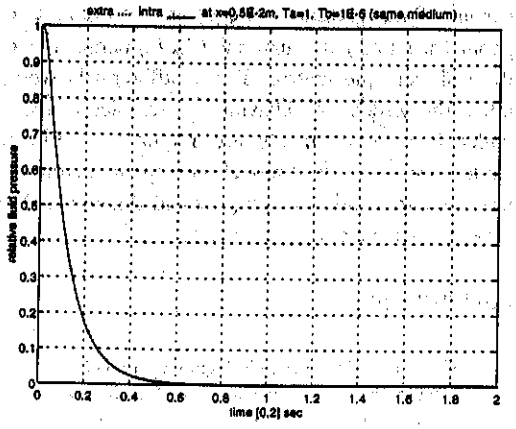

Figure 4. $R^{(i)}$ and $R^{(e)}$ at $x = 0.5$ cm for $T_\alpha = 1$ and $T_\beta = 10^{-6}$ (i.e. same medium).

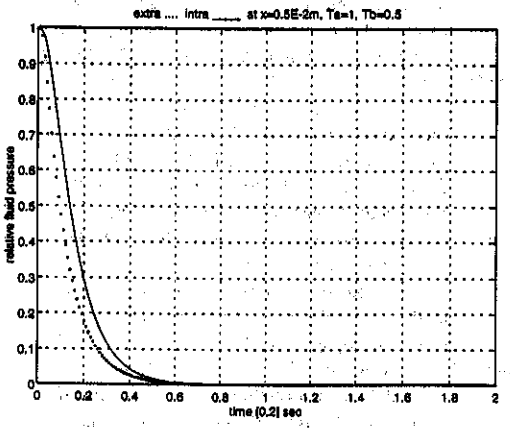

Figure 5. $R^{(i)}$ and $R^{(e)}$ at $x = 0.5$ cm for $T_\alpha = 1$ and $T_\beta = 0.5$.

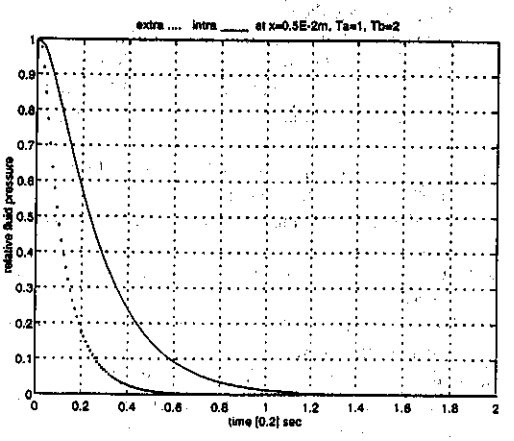

Figure 6. $R^{(i)}$ and $R^{(e)}$ at $x = 0.5$ cm for $T_a = 1$ and $T_b = 10^{-6}$.

Finally, a set of graphs for the behaviour of the solutions (5) and (6) at x=0.05 cm and with T_α = 200 and T_β = 10 have been developed in order to compare this solution to that obtained by Bachrach et al. (1995) for the case of a single poroelastic cell embedded in a poroelastic medium.

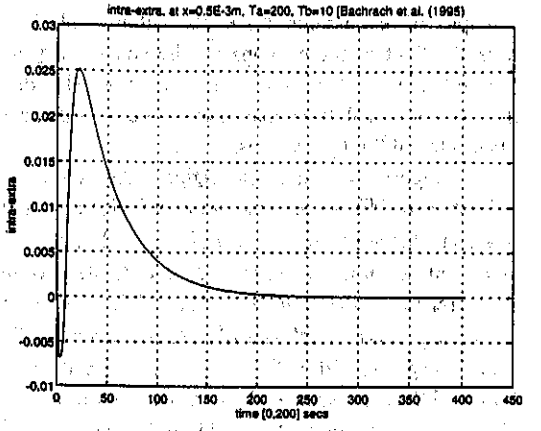

Figure 7. $R^{(i)} - R^{(e)}$ at $x = 0.05$ cm for $T_\alpha = 200$ and $T_\beta = 10$.

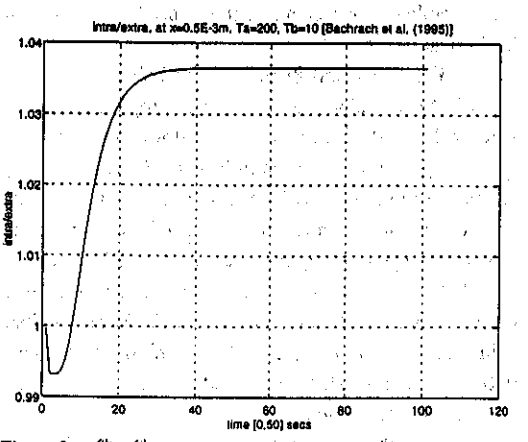

Figure 8. $R^{(i)}/R^{(e)}$ at $x = 0.05$ cm for $T_a = 200$ and $T_b = 10$.

6. DISCUSSION

The extracellular and intracellular fluid pressure distributions, shown in Figures 2 and 3, present substantial differences. While the extracellular pressure $R^{(e)}$ has the classical pronounced isochrones, the intracellular pressure $R^{(i)}$ has much less pronounced curves, especially near the boundaries of the sample. In those regions, $R^{(e)}$ decays rapidly while $R^{(i)}$ stays relatively high. This

difference creates a positive pressure differential between the intra-cellular and extra-cellular spaces, clearly due to the difference in material properties (T_α=1 and T_β=2) between cells and tissues.

This pressure differential is reminiscent of the 'secondary consolidation' phenomenon sometimes observed in geomechanics (Akagi 1994). This phenomenon has been linked to the existance of 'lumps' of exogenous materials within soil. The overall effect of these lumps on the soil is to delay the settlement of the sample under load; possibly due to the additional time that these take to dissipate their internal fluid presssures.

Figures 4, 5 and 6 investigate the behaviour of $R^{(e)}$ and $R^{(i)}$ for diverse geometrical (α,L) and material characteristics (T_α,T_β) of cells and tissue. As expected, when the paramertes T_α and T_β are chosen as to represent that cells and tissues have the same material properties, $R^{(i)}$ and $R^{(e)}$ are the same. As T_α and T_β begin to differ, $R^{(i)}$ and $R^{(i)}$ begin to diverge too. A difference, such as the one observed in Figure 6, where (T_α=1 and T_β=2) would imply that $\alpha = 10^{-4}$ and $\beta = 5\text{x}10^{-11}$. This is a large, but not an unthinkable, discrepancy that could occur in biological tissues.

Figures 7 and 8 present the behaviour of $R^{(i)}$ and $R^{(e)}$ for the characteristics of a sample studied by Bachrach et al. (1995). These authors investigated the compression of a chondrocyte (cartilage cell) within a sample of cartilage tissue. The behaviour of $R^{(i)}$–$R^{(e)}$, Figure 7, shows a differential with a peak of 2.5% occurying at approximately t = 25 seconds. $R^{(i)}/R^{(e)}$, Figure 8, shows that this quotient grows until reaching a steady-state of 1.037. Both of thse solutions present an acceptable level of agreement with Bachrach et al. (1995) who found less than 5% and ~1.025, respetively.

All these results are mechanically and biologically reasonable. However, only experiments will show if poroelasticity is a valid model for the beahviour of cells, or other models, such as tensegrity (Stamenovic et al. 1996) are more appropriate.

7. CONCLUSIONS & FUTURE WORK

The cellular poroelastic model predicts susbtantial differences between the intra-cellular and extra-cellular fluid pressures, depending on a set of geometrical (α,L) and material (T_α,T_β) parameters of the cells and the matrix. These differentials would affect the settlement behaviour of samples of tissue under load. Experiments are required to further explore this theoretical model, perhaps involving the use of confocal microscopy (Lee and Bader 1995) in order to observe compressing cells.

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