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A NOVEL MODEL OF DIABETIC FOOT ULCERATION BASED ON POROUS MEDIA MECHANICS

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INTRODUCTION

Recently a new computational model, based on the thermodynamically constrained averaging theory (TCAT), has been proposed to predict tumor initiation and proliferation [1, 2]. A similar mathematical approach is proposed here to model foot tissue mechanics and diabetic ulcer formation. The common aspects at continuum level between these two computational models are: the macroscopic balance equations governing tissue mechanics, fluid flow and diffusion of chemicals, and some of the constitutive equations.

THE TCAT PROCEDURE

TCAT [3] is a framework recently established for the analysis of multiphase systems, which is consistent over multiple scales. It provides a rigorous yet flexible method for developing multiphase, continuum models at any scale of interest. TCAT uses averaging theorems to formally and consistently convert micro-scale equations to the larger macro-scale. These averaging theorems convert averages of micro-scale derivatives into derivatives of macro-scale averages and share some features of the well-known transport and divergence theorems.

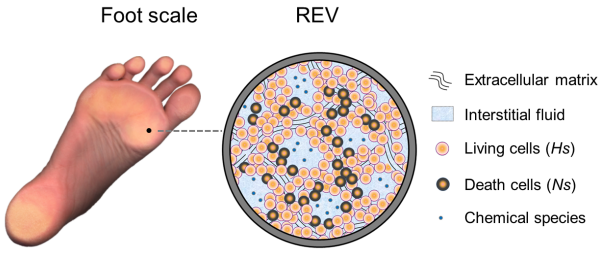

Figure 1: The multiphase system (on the right) and its relation with a macroscopic point (on the left).

Hence, the TCAT procedure explicitly defines larger scale variables in terms of smaller scale ones. The macroscale depends on the concept of the representative elementary volume (REV) (see Figure 1). REV is an averaging volume that can be centered at each point in the system and has to be large enough to include all present phases so that values of averages are independent of its size. The volume must also be much smaller than the length scale of the entire system (known as the megascale), so that quantities such as gradients are meaningful.

MATHEMATICAL MODEL

The foot tissue is modeled as an elastic porous medium in large strain regime completely filled by a fluid phase. The tissue cells and their extracellular matrix form the solid skeleton *s* with pores saturated by the interstitial fluid *f*. Indeed, the sum of the volume fractions for the two phases has to be unit

$$\varepsilon^s + \varepsilon^f = 1 \tag{1}$$

Being the pores fully saturated, the volume fraction of the interstitial fluid, ε^f, is equal to the porosity of the medium, which is denoted here as ε.

Transport of nutrients and possible drugs delivery within the microvasculature are also considered by means of the introduction of an effective diffusion coefficient which is estimated from the real degree of vascularisation of the zone of interest. The tissue may become necrotic depending on the stress level and on vasculopathy; thus it comprises a healthy fraction (*Hs*) and a necrotic one (*Ns*). Assuming that there is no diffusion of either necrotic and living cells the mass conservation equations of the healthy and necrotic fractions of the tissue read respectively

$$\frac{\partial\left(\varepsilon^s\rho^s\omega^{\overline{Hs}}\right)}{\partial t} + \nabla\cdot\left(\varepsilon^s\rho^s\omega^{\overline{Hs}}\mathbf{v}^{\bar{s}}\right) + \varepsilon^s r^{Ns} = 0 \tag{2}$$

$$\frac{\partial\left(\varepsilon^s\rho^s\omega^{\overline{Ns}}\right)}{\partial t} + \nabla\cdot\left(\varepsilon^s\rho^s\omega^{\overline{Ns}}\mathbf{v}^{\bar{s}}\right) - \varepsilon^s r^{Ns} + \overset{Ns\to f}{M} = 0 \tag{3}$$

where $\omega^{\overline{Hs}}$ is the mass fraction of the healthy tissue cells (and associated ECM), $\omega^{\overline{Ns}}$ is the mass fraction of the necrotic tissue cells (and associated ECM), ρ^s is the density of the tissue and $\mathbf{v}^s$ is the velocity of the solid phase. The term $\varepsilon^s r^{Ns}$ is the cells' death rate and represents an intra-phase exchange of mass (i.e. within the phase *s*). $\overset{Ns\to f}{M}$ is the

rate of dissolution of the necrotic cells and is an inter-phase exchange of mass (from the phase *s* to the phase *f*). Summing equations (2) and (3) gives the mass balance equation of the solid phase

$$\frac{\partial\left(\varepsilon^s\rho^s\right)}{\partial t}+\nabla\cdot\left(\varepsilon^s\rho^s\bar{\mathbf{v}}^s\right)+\overset{s\to f}{M}=0 \tag{4}$$

where $\overset{s\to f}{M}=\overset{Ns\to f}{M}$.

From TCAT, the mass conservation equation of the chemical species *i* in the interstitial fluid (phase *f*) reads

$$\begin{aligned}&\frac{\partial\left(\varepsilon^f\rho^f\bar{\bar{\omega}}^{if}\right)}{\partial t}+\nabla\cdot\left(\varepsilon^f\rho^f\bar{\bar{\omega}}^{if}\bar{\mathbf{v}}^f\right)+\\&+\nabla\cdot\left(\varepsilon^f\rho^f\bar{\bar{\omega}}^{if}\bar{\bar{\mathbf{u}}}^{if}\right)-\overset{is\to if}{M}=0\end{aligned} \tag{5}$$

where $\bar{\bar{\omega}}^{if}$ is the mass fraction of the species *i* dispersed within the phase *f*, $\overset{is\to if}{M}$ is an inter-phase exchange term (mass of the chemical species *i* consumed or relaxed by the tissue) and $\bar{\bar{\mathbf{u}}}^{if}$ is the diffusive velocity of the species *i*. Summing equation (5) over all species gives the mass balance equation of the interstitial fluid

$$\frac{\partial\left(\varepsilon^f\rho^f\right)}{\partial t}+\nabla\cdot\left(\varepsilon^f\rho^f\bar{\mathbf{v}}^f\right)=\overset{s\to f}{M} \tag{6}$$

It is assumed that the mass of chemical substances consumed by the cells is equal to that produced due to their metabolism, therefore the tissue does not growth. However it may dissolve due to cells necrosis. Hence the source term in equation (6) reads

$$\overset{s\to f}{M}=\begin{cases}\sum_{i\in f}\overset{is\to if}{M}=0 & \text{in a healthy tissue}\\ \sum_{i\in f}\overset{is\to if}{M}>0 & \text{when necroisis occurs}\end{cases} \tag{7}$$

From TCAT the relative velocities of the interstitial fluid phase *f* reads [2]

$$\bar{\mathbf{v}}^f-\bar{\mathbf{v}}^s=-\frac{\mathbf{k}^{fs}}{\mu^f\varepsilon^f}\nabla p^f \tag{8}$$

where $\mathbf{k}^{fs}$ and μ^f are the intrinsic permeability tensor and the dynamic viscosity respectively, and p^f is the interstitial fluid pressure (IFP). IFP increases instantaneously when the foot comes into contact with the ground, then, after a while, the stress is transferred onto the solid matrix following a well-known mechanism which in geomechanics is called consolidation.

With respect to the effective stress principle [4], the linear momentum balance of the solid phase in a rate form is

$$\nabla\cdot\left(\frac{\partial\bar{\bar{\mathbf{t}}}^s_{eff}}{\partial t}-\frac{\partial\left(\alpha p^f\right)}{\partial t}\mathbf{1}\right)=0 \tag{9}$$

where α is the Biot's coefficient and $\bar{\bar{\mathbf{t}}}^s_{eff}$ is the effective stress in the sense of porous media mechanics.

NUMERICAL SOLUTION

To obtain a solvable system of equations, some constitutive equations are introduced in the general governing equations of the previous paragraph. These equations regulate cells' metabolism, necrosis, diffusion of chemicals species within the interstitial fluid and tissue mechanics. More in detail, the foot tissue is modeled as an elastic porous medium in large strain regime. The assumption of relatively slow velocities allow to neglect inertial forces and simplify the mathematical formulation; in other words the problem is considered quasi-static. Using an adequate time step the numerical results reproduce exhaustively the experimental ones. However in the next future, numerical test will be performed to investigate more in detail the dynamic behavior of the system and the influence of the inertial forces on the computed solution. The assumed boundary conditions are consistent with experimental measurements performed at the mega level: in-vivo kinematics, kinetics and magnetic resonance are the input data of the model [5].

The primary variables of the model are: the IFP, p^f, the velocity vector of the solid phase $\mathbf{v}^s$, and the mass fraction of oxygen, $\bar{\omega}^{Of}$. The latter together with the stress in the tissue regulates cells' metabolism and the occurrence of ulceration. With respect to these primary variables the governing equations are discretized in space by the finite element method [4], in time domain using the θ-Wilson method and then solved numerically.

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