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Preliminaries for a New Mathematical Framework for Modelling Tumour Growth Using Stress State Decomposition Technique

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Abstract

The main goal of the present paper is to present a mathematical framework for modelling tumour growth based on stress state decomposition technique (SSDT). This is a straightforward extension of the model for multi-phase non-saturated soil consolidation with pollutant transport presented by the authors and may be regarded as an alternative to classical frameworks based on TCAT theory. In this preliminary work, the Representative Volume Element (RVE) for tumour is proposed along with its comparison with the corresponding one for soils modelling developed formerly by the authors. Equations standing for tumour phase are flawlessly brought into correspondence with those of gaseous phase in the soil problem showing that a similar task may be carried out for the remainders phases taking part in both RVEs. Furthermore, stresses induced by nonlinear saturation and permeability dependence on suction for soil interstitial fluids transport finds its counterpart on the contact between the cancer cell membrane and interstitial fluids rendering a higher primary variables coupling degree than what was attained in TCAT theory. From these preliminaries assessments, it may be put forward that likewise the stress state decomposition procedure stands for an alternative for modelling multi-phase nonsaturated soil consolidation with pollutant transport; it does for modelling cancer as well.

Keywords

Cancer, Tumour Growth, Mathematical Modelling,
Stress State Decomposition Technique

1. Introduction

According to [1], cancer has been known since human society first recorded

their activities. It was well known to the ancient Egyptians and to succeeding civilizations but, as most cancers develop in the latter decades of life, the decease became a real issue when life expectation began to grow. It was the German microscopist, Johannes Mueller, who showed that cancers were made up of cells, a fundamental discovery that would change the way humanity would address the search for a definite healing. In [2] is remarked that the early work on diffusion in tissues [3] set the scene for many later mathematical models of solid tumours. Through this paper, the process of diffusion of dissolved substances in cells and tissues becomes a determining subject in vital processes. Furthermore, a mathematical approach to study a number of important physiological processes, was also developed. However, the upcoming years will witness the springing up of solid tumours models focused purely in growth dynamics.

The pioneer work in [4], settled the basis for treating multicellar spheroid as a standard in vitro system used to evaluate the uncontrolled duplication rate of a tumour cell aggregate. By losing the aptitude to self-regulation by apoptosis mechanism, they tend to reproduce themselves an uncontrolled fashion commonly isotropically resulting in a nearly spherical shape. Reference [5] compared these experimental results with a model to investigate the roles of both nonuniform mitotic inhibition and geometry on the stability of growth. However, the necrosis mechanism was not considered, then stability only occurred by complete growth inhibition throughout the tissue. In [6], the necrotic core was simply incorporated as a source of growth inhibition. In the early 1990s, [7] proposed a mathematical paradigm that paves the way for modeling the mechanisms of cell migration.

Hinged on [8] [9] and [10], the mathematical theory of multiphase model was applied to cancer simulation. One of the first multiphase models was proposed by [11]. These authors considered two incompressible phases: 1) Tumour cells, behaving inviscidly; 2) Extracellular water. It must be underscored that no surface tension was regarded. Reference [12] presented a model for tissue growth, in which the swelling of the solid (cellular) phase feeding by extracellular fluid in clear opposition to consolidation process however resembling the underlain mechanism with mass exchange. For these purposes, a constitutive rule connecting mass exchange and solid skeleton expansion. Furthermore, in [13] principles of solids mechanics were regarded and the Darcy's law for pressure gradients was incorporated as well. Reference [14] concluded that the concept of volume fraction and the essentials of the multiphase continua must be introduced and applied to the problem. The system of equations and its validity was discussed with the aid of numerical simulations.

Reference [15] pointed out the role of mechanical stress in the growth of multicell spheroids. They also developed a theoretical framework for volumetric growth suitable for modeling the growth of soft tissues exhibiting the properties of a solid.

Reference [16], poses that the relationship between growth and stress in tumours, indubitably brought into evidence by experimental facts, still remains in

shadows. Both, the constitutive equations of cancer cell and the growth law relating stress and mitosis-apoptosis, weren't clearly identified. However it was shown that solid tumours exhibit several mechanical features of a poroelastic material, where the cellular component behaves like elastic solid as well as novel approach for assessing nonhomogeneous growth and residual stress in spherical domains.

In [17], an extension of a multiphase porous media model based on TCAT theory ([18]) to tumour growth was presented. Treating the tumour mass as a multiphase medium composed of an extracellular matrix; tumour cells, which may become necrotic depending on the nutrient concentration and tumour phase pressure; healthy cells; and an interstitial fluid for the transport of nutrients, the resulting equations were solved by FEM. Reference [19] shows how the cancer decease may be tackled by a totally different viewpoint, *i.e.*, decoupling the equations in order to avoid numerical simulation.

An alternative to mixture theory ([12] [17]) and volume fraction concept for modelling consolidation in nonsaturated porous media was presented in [20]. Here, a stress state decomposition technique (SSDT) brought forth the differential equations that efficiently solve the environmental issue using the stress analysis instead of the mixture theory. These different stress states were selected in order to provide a physical meaning to the effective parameters arose in the extended Biot's equation. The matric suction coupling effect was also regarded.

In the present manuscript, an extension of the mathematical framework appeared in [20], is carried out. Hinged on the very same stress decomposition structure, the different constituents of the representative soil portion are paralleled with those standing for the cancer representative one however bewaring to preserve the substantial difference, *i.e.* the cell mitosis, cell influx of extracellular fluid, etc.

2. The Governing Equations

2.1. Introduction

Mathematical modelling of tumour as well as nonsaturated soil consolidation may be carried out at different length scales. Whether the continuum hypothesis is to be preserved, all phases must be present in the selected volume of multiphase media (RVE), *i.e.*, it must render to a straightforward idealization of the whole biological system. For the present work is centered on the aforementioned hypothesis, the more suitable scale for multiphase systems is the macroscale. At this level, the constituent parts of main concern are (**Figure 1**): The Extracellular Matrix (ECM) is the main component of the stroma (a sub-epithelial structure holding endothelial cells, fibroblast and blood vessels) and, for the model, considered as a solid phase that gives structure for the other phases. Healthy Cells (HC) and Tumour Cells (TC) are regarded as fluid phases. Finally, the Interstitial Fluid (IF) (mainly water) is another liquid phase however specialized for providing nutrients to cells and the media for cell signaling, a unique process that aims to control

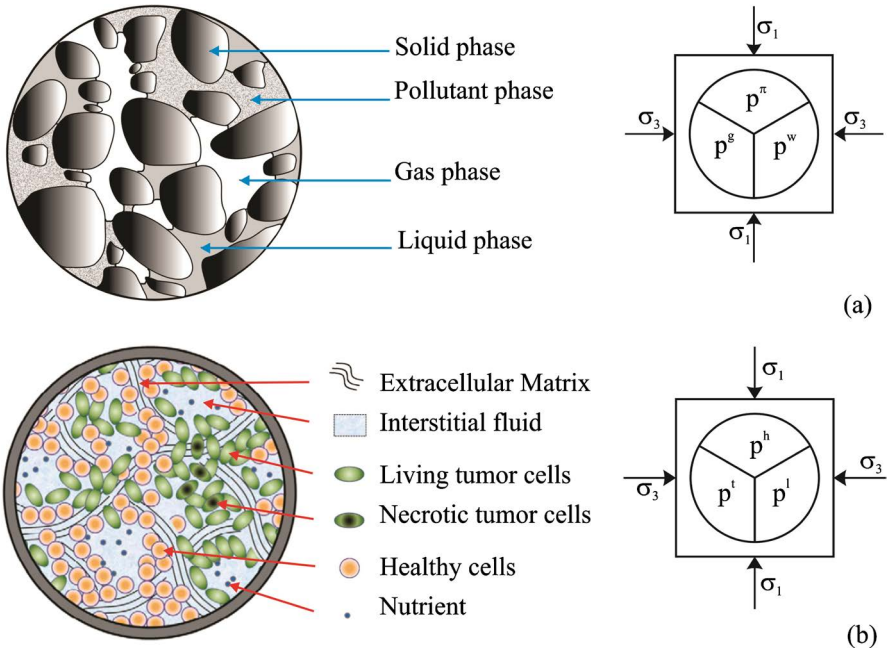

Figure 1. (a) Nonsaturated soil RVE. (b) Tumour growth RVE.

growth and necrosis of HC. The dependence cell-matrix with respect to tumour progression is macroscopically simulated by suction-like forces and mass exchange through membranes. This line of attack may be paired with TCAT theory considering that both take over interactions between two or more fluid and solid phases occupying a shared domain. Therefore, a system of equations consisting of mass and momentum balance for each phase, mass and momentum exchange between phases, and appropriate constitutive laws to close these equations, is attained.

2.2. TCAT-Based Tumour Phase Equation

For tumour growth, the development of the governing equations is carried out by averaging from micro to macro scale and by using closure techniques to parameterize the resulting equations.

However different in the number of relevant phases, analogous procedures to those brought into consideration in multiphase transport problems are regarded. A remarkable one is phase contact solution hereinbelow succinctly mentioned.

As previously pointed out, the ECM is regarded as a porous solid with porosity ε, being the corresponding volume fraction $\varepsilon^s = 1-\varepsilon$. The remaining volume will be filled by tumour cells TC ε^t, healthy cells HC (ε^h) and interstitial fluid IF (ε^l). The overall volume fractions must add to unity ($\varepsilon^s + \varepsilon^h + \varepsilon^t + \varepsilon^l = 1$), for consistence purposes. Accordingly, each phase saturation equation is $S^\alpha = \varepsilon^\alpha / \varepsilon$, which in turn leads to $S^h + S^t + S^l = 1$.

The mass balance for any α phase ([17]):

$$\frac{\partial\left(\varepsilon^\alpha \rho^\alpha\right)}{\partial t} + \nabla\cdot\left(\varepsilon^\alpha \rho^\alpha \mathbf{v}^{\bar{\alpha}}\right) - \overset{k\to\alpha}{M} = 0 \tag{1}$$

where: ε^{α} is the volume fraction of α phase; ρ^{α} is the density of α phase; $\boldsymbol{v}^{\bar{\alpha}}$ is the velocity of α phase; M is the interface exchange mass and $\sum_{K\in\Im_{c\alpha}}$ is summation symbol over all interfaces exchanging mass.

Considering the tumour phase made up of a necrotic phase (mass fraction ω^{Nt}) and of a growing living cells phase (mass fraction $1-\omega^{Nt}$), the mass equation for tumour phase is:

$$\frac{\partial\left(\varepsilon^{t}\rho^{t}\right)}{\partial t}+\nabla\cdot\left(\varepsilon^{t}\rho^{t}\boldsymbol{v}^{t}\right)-\overset{l\to t}{M}=0 \tag{2}$$

From the constitutive equations for tumour phase, the relative velocity of this phase:

$$\boldsymbol{v}^{t}-\boldsymbol{v}^{s}=-\frac{k_{rel}^{\alpha s}\boldsymbol{k}^{\alpha s}}{\mu^{\alpha}\left(\varepsilon^{\alpha}\right)^{2}}\nabla p^{t}=K\nabla p^{t} \tag{3}$$

Being, $\boldsymbol{v}^{t}$ the tumour velocity, $\boldsymbol{v}^{s}=\partial u^{s}/\partial t$ the ECM velocity; $k_{rel}^{\alpha s}$ relative permeability with respect to solid phase; $\boldsymbol{k}^{\alpha s}$ absolute permeability; μ^{α} mass density and p^{t} tumour pressure. The absolute permeability tensor is a function of the degree of cell adhesion to the ECM. This concept, apparently very different from the one commonly posed in soil mechanics, may be nonetheless associated to common permeability in porous media.

Substituting Equation (3) in Equation (2) and disregarding the density gradient of tumour phase (because of the scant value of prevailing pressures) along with the substitution of volume fraction by εS^{t}, finally leads to the governing equation for tumour phase:

$$\frac{\partial\left(\varepsilon S^{t}\right)}{\partial t}+\nabla\cdot\left(\varepsilon S^{t}\frac{\partial u^{s}}{\partial t}\right)-\nabla\cdot\left(\frac{k_{rel}^{ts}\boldsymbol{k}^{ts}}{\mu^{t}}\nabla p^{t}\right)=\frac{\overset{l\to t}{M}}{\rho^{t}} \tag{4}$$

Equation (4) is one of the various that furnished the TCAT-based framework for modelling tumour growth. Excellent computational outcomes were obtained using this equation in tumor simulations, in total agreement with experimental results [17].

For the scopes of the present paper, no other equation will be written out (see [17] for a complete perspective).

2.3. Geomechanics-Based Gaseous Phase Equation

In order to set down the tumour phase equations for SSDT-based formulation, a different approach must be carried out. Thought either the TCAT-based or SSDT-based viewpoint rely on geotechnical concept grounds, the later tenet is to set up a suitable idealization of the RVE in which different stress states are selected (**Figure 1**) in order to link all the internal variables arisen in the modelization process to those selected as primary. In brief, the SSDT is a technique that provides additional equations whenever are required (see [20] for a complete description of SSDT).

For the scope of the present, the equivalent of Equation (4) will be written out. The starting point is a mass balance equation as well. Here, the balance is brought about the fluid phases present in partially saturated soil consolidation process ([21]):

$$\frac{\partial\left(nS_{\pi}\rho^{\pi}\right)}{\partial t}+div\left(nS_{\pi}\rho^{\pi}\boldsymbol{v}^{\pi}\right)=\pm\dot{m} \tag{5}$$

Being $S_{\pi},\rho^{\pi},v_{\pi}$, π phase saturation, density and velocity respectively; $\dot{m}$ rate of mass transferred and n porosity.

In two-phase systems, the right hand side in the previous is negative for water phase and positive for gaseous phase.

For reasons hereinafter clarified, the tumour phase will be equated to geotechnical problem gaseous phase. This choice is hinged on the fact that the liquid phase, a priori more suitable from tumour physical standpoint, will be set aside to be equated to interstitial fluid phase. Therefore, the gaseous phase equation is, [20]:

$$\frac{\partial\left(nS_{g}\rho^{g}\right)}{\partial t}+div\left(nS_{g}\rho^{g}\boldsymbol{v}^{g}\right)=\overset{l\to g}{m} \tag{6}$$

Considering Darcy's law:

$$\boldsymbol{v}_{gr}=-\frac{k_{g}}{\mu}\nabla p^{g} \tag{7}$$

With k_{g} and μ; being gas permeability and gas density respectively. Furthermore, introducing the relative velocity $\boldsymbol{v}_{gr}=n_{g}\left(\boldsymbol{v}_{g}-\boldsymbol{v}_{s}\right)$ in Darcy's law, results in:

$$\boldsymbol{v}_{g}=\frac{\boldsymbol{v}_{gr}}{n_{g}}+\boldsymbol{v}_{s}=-\frac{k_{g}}{\mu\, nS_{g}}\nabla p^{g}+\frac{\partial u_{s}}{\partial t} \tag{8}$$

Finally, putting the previous in Equation (6), leads to:

$$\frac{\partial\left(nS_{g}\right)}{\partial t}+\nabla\cdot\left(nS_{g}\frac{\partial u_{s}}{\partial t}\right)-\nabla\cdot\left(\frac{k_{g}}{\mu}\nabla p_{g}\right)=\frac{\overset{l\to g}{m}}{\rho^{g}} \tag{9}$$

Equation (9) stands for the mass balance equation for gaseous phase provided that the multiphase soil consolidation problem is regarded.

2.4. SSDT-Based Equations as an Alternative to TCAT-Based Equations

With the aim of likening the previous equation with Equation (4) and thereby pose an alternative mathematical formulation for tumour growth, some remarks must be furthered.

According to **Figure 1**, wherein the soil RVE is brought into correspondence with tumour RVE, it is clear that both processes may be modeled with similar mathematical tools as long as the schematics representations on the right are deemed. Furthermore, both schematics representation (for soils and for cancer)

show the set of stresses that would be involved if the stress state decomposition is to be brought under consideration.

Specifically, in the schematic RVE for soil, p^g, p^π, p^w stand for gas, pollutant and water pressure respectively, meanwhile in the schematic RVE for cancer, p^g, p^π, p^w stand for tumour, healthy cells and interstitial fluid pressure respectively. This idealization allows matching p^g with p^t (and so on with the remaining phases) and whereby the justification for matching the gaseous phase with tumour phase is now clearly evident.

In the light of this, Equation (9) may be slightly reformulated in the following manner:

$$\frac{\partial\left(nS_t\right)}{\partial t}+\nabla\cdot\left(nS_t\frac{\partial u_s}{\partial t}\right)-\nabla\cdot\left(\frac{k_t}{\mu}\nabla p_t\right)=\frac{\overset{l\to t}{M}}{\rho^t} \tag{10}$$

where the gaseous phase indicator, *g*, was replaced by the tumour one, *t* and the uppercase letter was used for mass indicator. With this minor change, both Equation (4) and Equation (10) are absolutely tantamount ($\varepsilon \equiv n$ as well as $k_{rel}^{ts}\boldsymbol{k}^{ts} \equiv k_t$) and it is a remarkable fact considering that both are derived from absolutely different standpoints. Needless to remark that out of Equation (10), the same concordance with experimental results obtained with Equation (4) in [17] is expected.

Furthermore, this outcome paves the way to carry out the same transformation for the remaining relevant phases (*i.e.* ICM, HC and IF), in a more appropriate form for stress state combination approach and therefore a complete alternative for TCAT theory may be furthered. Moreover, according to what was achieved for soil consolidation modelling with SSDT, it may be expected that a higher degree of coupling between relevant variables is obtained when compared with TCAT theory. However the complete formulation regarding coupled equations and all the involved stress states will be subject of forthcoming presentations.

3. Concluding Remarks

A general however preliminary mathematical idealization of tumour growth in an extracellular matrix with the presence of healthy cells based on stress state decomposition technique was presented as an alternative to thermodynamically constrained theory.

Moreover and specifically, the derivation of tumour phase conservation equation using the environmental geomechanics modelling as starting point was carried out as well. In addition, schematic representation of RVE for cancer was introduced as a natural extension of unsaturated soil RVE.

Due to the fact that tumour phase equations derived either for TCAT or SSDT frameworks are flawlessly brought into correspondence, it may be expected that a similar task could be carried out for the remainders phases taking part in both RVEs resulting in a complete system of highly coupled differential equations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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