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Simulation of angiogenesis in a multiphase tumor growth model

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Highlights

- We introduce in our multiphase model for avascular tumor growth two new species.
- The new species are the tumor angiogenic factor (TAF) and endothelial cells (EC).
- Their diffusion and interaction simulate angiogenesis.
- Two numerical simulations of angiogenesis are proposed.
- The new capillary network will allow for simulating the chemotherapeutic agents delivery.

Abstract

The avascular multiphase model for tumor growth, developed by the authors in previous works, is enhanced to include angiogenesis. The original model comprises the extracellular matrix (ECM) as porous solid phase and three fluid phases: living and necrotic tumor cells (TCs), host cells (HCs), and the interstitial fluid. In this paper we add transport of tumor angiogenic factor (TAF) and of endothelial cells. The density of the endothelial cells represents the newly created vessels in a smeared manner. Co-opted blood vessels can be added as line element with flow or can be taken into account as boundary condition. The model is hence of the continuum–discrete type. Two examples show the potential of the newly enhanced model. The first deals with growth of a 2D tumor spheroid in a square tissue domain. From a blood vessel, posed on one side of the domain, angiogenesis takes place through the migration of endothelial cells from the vessel to the tumor. The second one is the simulation of cutaneous melanoma growth with the diffusion of TAF from the living tumor cells and the consequent development of a new vessel network, represented by the endothelial cells density. The introduction of angiogenesis will allow for simulating the delivery of chemotherapeutic and nanoparticle-mediated agents to the vascular tumor, and for evaluation of the therapeutic effect.

Keywords: Porous media mechanics; Multiphase system; Finite element method; Tumor growth; Angiogensis; Melanoma

1. Introduction

Angiogensis is the formation of new vessels from the existing vasculature. It is of fundamental importance in many physiological processes such as normal tissue growth, embryonic development, wound healing, and pathological

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Nomenclature

eqn.	Equation
eqs.	Equations
TCAT	Thermodynamically Constrained Averaging Theory
a	Coefficient in the pressure–saturations relationship
$\mathbf{C}_{ij}$	Nonlinear coefficient of the discretized capacity matrix
$\mathbf{d}^{\bar{\bar{\alpha}}}$	Rate of strain tensor
$D^{\overline{il}}_{eff}$	Effective diffusion coefficient for the species i dissolved in the phase l
EC	Endothelial cells
$\mathbf{f}_v$	Discretized source term associated to the primary variable v
$\mathbf{K}_{ij}$	Nonlinear coefficient of the discretized conduction matrix
K_i	Compressibility of the phase i ($i = s, t, h$ and l)
$\mathbf{k}$	Intrinsic permeability tensor of the ECM
k^{α}_{rel}	Relative permeability of the phase α
$\mathbf{N}_v$	Vector of shape functions related to the primary variable v
p^{α}	Pressure in the phase α
p^{ij}	Pressure difference between fluid phases i and j
S^{α}	Saturation degree of the phase α
$\mathbf{t}^{\bar{\bar{s}}}_{eff}$	Effective stress tensor of the solid phase s
$\mathbf{t}^{\bar{\bar{s}}}$	Total stress tensor of the solid phase s
$\mathbf{t}^{\bar{\bar{s}}}_{eff,y}$	Yield limit of the solid phase which defines the boundary of elastic domain
TAF	Tumor angiogenic factors
$\mathbf{u}^{s}$	Displacement vector of the solid phase s
$\mathbf{v}^{\bar{\alpha}}$	Velocity vector of the phase α
$\mathbf{x}$	Solution vector
$\bar{\alpha}$	Biot's coefficient
γ^{t}_{growth}	Growth coefficient
$\gamma^{t}_{necrosis}$	Necrosis coefficient
$\gamma^{\overline{nl}}_{growth}$	Nutrient consumption coefficient related to growth
$\gamma^{\overline{nl}}_{0}$	Nutrient consumption coefficient not related to growth
ε	Porosity
ε^{α}	Volume fraction of the phase α
η	Viscosity parameter of the solid phase
μ^{α}	Dynamic viscosity of the phase α
ρ^{α}	Density of the phase α
σ_{ij}	Interfacial tension between fluid phases i and j
ψ^{α}	Adhesion of the phase α
$\omega^{N\bar{t}}$	Mass fraction of necrotic cells in the tumor cells phase
$\omega^{\overline{nl}}$	Nutrient mass fraction in the interstitial fluid
$\omega^{\overline{nl}}_{crit}$	Critical nutrient mass fraction for growth
$\omega^{\overline{nl}}_{env}$	Reference nutrient mass fraction in the environment
$\omega^{\overline{TAF}}$	TAF mass fraction in the interstitial fluid
$\omega^{\overline{TAF}}_{crit}$	Critical TAF mass fraction
$\omega^{\overline{EC}}$	Endothelial cells mass fraction in the interstitial fluid
$\omega^{\overline{EC}}_{crit}$	Critical endothelial cells mass fraction for the death of the endothelial cells
ν_{TAF}	Coefficient for uptake of TAF by endothelial cells
β_{TAF}	Degradation rate coefficient for TAF demise
c	Coefficient for TAF and endothelial cells production