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Variation of different growth descriptions in a metastatic proliferation model

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Micro Abstract
In biological tissue, the proliferation of metastases is governed by nutrient-driven cell division. In a continuum-mechanical model based on the Theory of Porous Media, the proliferation is described via mass production terms. Therein, the constitutive approach for the growth of the metastases is implemented either by a Monod-type or a logistic growth function. In both cases, the results are compared to cancer-cell-growth experiments.

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Introduction

The proliferation of cancer cells in biological tissue such as the brain tissue can be described by a Monod-type equation or a logistic growth (Verhulst-type) equation, cf. [4,5]. The Monod-type equation relates the growth rate to the nutrient concentration, whereas in the Verhulst-type equation the cancer-cell concentration is the driving force. In this contribution, a continuum-mechanical model of cancer-cell proliferation implements these equations as mass-production terms and gives the possibility to compare simulation results to in-vitro experimental data of lung-cancer cells, which are capable of metastasing the brain.

Metastatic proliferation model

The fundamental framework of the multi-component continuum-mechanical model is given by the Theory of Porous Media (TPM), cf. [2]. Therein, superimposed and interacting continua stem from the volumetric homogenisation of the microstructure in a representative elementary volume. In particular, the constituents φ^α of the model are the liquid-saturated solid skeleton φ^S, namely the brain cells, and the two immiscible pore liquids φ^β, where $\beta = \{I, B\}$ represent the interstitial fluid φ^I and the blood φ^B. Furthermore, the interstitial fluid is described as a real mixture of interacting components $\varphi^{I\gamma}$. Therein, the proliferation and basal reactions of the cancer cells φ^{IC} are decreasing the nutrients φ^{IN} and gain their mass from the solvent φ^{IL}. As a result, mass-production terms are included in the governing balance equations of mass and momentum. In particular, the adapted governing equations are given by the concentration balance for φ^{IC} and φ^{IN} $(1)_1$, the volume balances for φ^β $(1)_2$ and the overall momentum production $(1)_3$, yielding

$$\begin{aligned}
0 &= n^I (c_m^{I\gamma})'_S + \operatorname{div}(n^I c_m^{I\gamma} \mathbf{w}_{I\gamma}) + c_m^{I\gamma}(\operatorname{div}(n^B \mathbf{w}_B) + \operatorname{div}(\mathbf{u}_S)'_S) - \frac{\hat{\rho}^{I\gamma}}{M_m^{I\gamma}}\,, \\
0 &= (n^\beta)'_S + \operatorname{div}(n^\beta \mathbf{w}_\beta) + n^\beta \operatorname{div}(\mathbf{u}_S)'_S\,, \\
\mathbf{0} &= \operatorname{div} \textstyle\sum_\alpha \mathbf{T}^\alpha + \rho\,\mathbf{g} \quad \text{with} \quad \textstyle\sum_\alpha(\hat{\mathbf{p}}^\alpha + \hat{\rho}^\alpha \mathbf{x}'_\alpha) = \sum_\alpha \hat{\mathbf{s}}^\alpha = \mathbf{0}\,.
\end{aligned} \tag{1}$$

Therein, the volume fraction of φ^I is referred to its solvent $n^I \approx n^{IL}$ and the solid volume fraction is integrated resulting in $n^S = n_0^S J_S^{-1}$, where J_S^{-1} is the Jacobian determinant of the

solid. Furthermore, $(\cdot)'_S$ is the material time derivative with respect to the solid. Besides the solid deformation $\mathbf{u}_S$, the primary variables of the system are the partial pore-liquid pressures p^{IR} and p^{BR} as well as the concentrations c_m^{ID} and c_m^{IN}. In the closure of the system, the entropy inequality is evaluated leading to the constitutive setting of the model. The seepage velocities $\mathbf{w}_\beta$ of the pore liquids and the seepage velocities of the components $\mathbf{w}_{I\gamma}$ can be identified as Darcy-like, respectively Fick-like equations, viz.:

$$n^\beta \mathbf{w}_\beta \,=\, -\,\frac{\mathbf{K}^{S\beta}}{\mu^{\beta R}}\,[\,\mathrm{grad}\, p^{\beta R} \,-\, \rho^{\beta R}\,\mathbf{g}\,] \quad \text{and} \quad n^I c_m^{I\gamma}\mathbf{w}_{I\gamma} \,=\, -\,\mathbf{D}^{I\gamma}\,\mathrm{grad}\, c_m^{I\gamma} \,+\, n^I c_m^{I\gamma}\mathbf{w}_I\ . \tag{2}$$

In (2), $\mathbf{K}^{S\beta}$ indicates the second-order intrinsic permeability tensor and $\mathbf{D}^{I\gamma}$ refers to the diffusivity. Moreover, the body force $\mathbf{g}$ corresponds to the gravity and $\mu^{\beta R}$ is the effective shear viscosity. Evaluating the summed stresses $\sum_\alpha \mathbf{T}^\alpha = \mathbf{T}^S_{E\,mech} - p\,\mathbf{I}$ reveals the composition of the overall pore liquid pressure $p = s^I p^{IR} + s^B p^{BR}$, where $s^\beta = n^\beta/(1-n^S)$ is the saturation, and $\mathbf{T}^S_{E\,mech}$ the mechanical extra stress of the solid. In particular, $\mathbf{T}^S_{E\,mech}$ is described by a neo-Hookean model, cf. [3].

Constitutive equations for proliferation

The model is assumed to be a closed system restricting the overall mass production $\sum_\alpha \hat{\rho}^\alpha = 0$. Nevertheless, individual components are able to gain or lose mass, cf. [7]. Herein, the cancer cells proliferate and gain mass $\hat{\rho}^{IC}_\oplus$. As a result of the basal cancer cell reactions and the growth process, nutrients are consumed and decline in mass $\hat{\rho}^{IN}_\ominus$. The nutrient consumption provides the energy for the proliferation, whereas the required mass for the cell division corresponds to the decline of the interstitial fluid solvent $\hat{\rho}^{IL}_\ominus = \hat{\rho}^{IC}_\oplus - \hat{\rho}^{IN}_\ominus$. The interplay between the gain and loss ensures the above mentioned closed system restriction by $\hat{\rho}^I = -\,\hat{\rho}^{IL}_\ominus + \hat{\rho}^{IC}_\oplus - \hat{\rho}^{IN}_\ominus = 0$. In particular, $\hat{\rho}^{IN}_\ominus$ is proportional to the cancer-cell concentration and its mass-production term.
Furthermore, a Monod-type equation and a Verhulst-type equation are applied to the mass-production term of the cancer cell and later on compared to lung cancer cell-growth experiments. The Monod-type equation explicitly relates the mass-production term $\hat{\rho}^{IC}_\oplus$ to the nutrient concentration, cf. Figure 1 **a**. Besides, the cancer cells require a sufficient nutrient concentration $\bar{c}_m^{IN}$ to sustain their proliferation, viz.:

$$\hat{\rho}^{IC}_\oplus \,=\, c_m^{IC} M_m^{IC} \mu^{IN}_\oplus \frac{c_m^{IN} - \bar{c}_m^{IN}}{K^{IN} + c_m^{IN} - \bar{c}_m^{IN}}. \tag{3}$$

Therein, K^{IN} is the nutrient concentration at $\mu^{IN}_\oplus/2$ and M_m^{IC} resembles the molar mass of the cancer cells. Moreover, the specific growth rate $\mu^{IN}_\oplus$ changes according to the amount of the cancer cells. This property originates from the spatial arrangement of the proliferating cells in a spheroid, where cells proliferate less in the centre, cf. [1].
Moreover, the Verhulst-type equation is proportional to the cancer cell concentration c_m^{IC}, cf. Figure 1 **b**, yielding

$$\hat{\rho}^{IC}_\oplus \,=\, c_m^{IC} M_m^{IC} \kappa^{IC} (1 \,-\, \frac{c_m^{IC}}{\bar{c}_m^{IC}}), \tag{4}$$

where κ^{IC} resembles the proliferation rate and $\bar{c}_m^{IC}$ is the highest possible cancer-cell concentration referring to the initiation of a macrometastasis.

Comparison to experimental data

For the comparison of the introduced proliferation descriptions, the adapted governing equations are transformed to their weak forms and are numerically solved for the primary variables within the FE tool PANDAS. Therein, Taylor-Hood elements are applied for the spatial discretisation

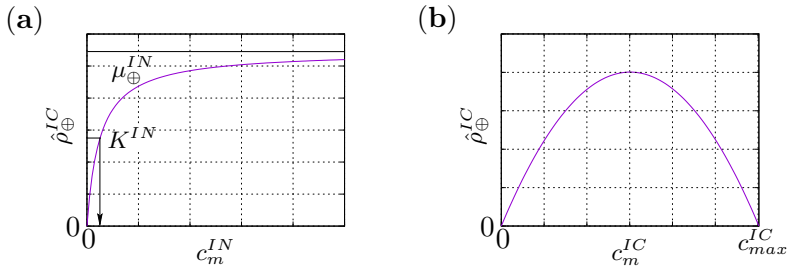

Figure 1. (**a**) Monod-type equation approaches the specific growth rate $\mu_{\oplus}^{IN}$ and is dependent of c_m^{IN} and the constant K^{IN}. (**b**) The Verhulst-type equation has a maximum at $\bar{c}_m^{IC}/2$, reaches zero for the extremes and is dependent on c_m^{IC}, the maximum concentration $\bar{c}_m^{IC}$ and the constant κ^{IC}.

and an implicit Euler time-integration scheme for the temporal discretisation. In the initial-boundary-value problem, cancer cells are seeded in the centre of a circular domain and start to migrate and proliferate. The nutrient concentration is fixed at the outer boundaries and gets reduced according to its mass-production term during the proliferation process. Consequently, a time series of cancer-cell concentration is generated.

Concerning the lung-cancer experiments, the volumetric proliferation data of the lung-cancer spheroids are averaged from four different proliferation series including five to eleven cancer-cell spheroids.

For the comparison between the simulations and the experimentals, a comparative scalar, namely the total number of cells N_{total}^{IC}, is identified.

For this purpose, the cancer-cell concentration of the continuum-mechanical model c_m^{IC} is related to the local bulk fluid volume $\mathrm{d}v^I = n^I \mathrm{d}v$, the molar mass of the cells M_m^{IC} and the number of cells per volume M^{IC}, cf. [6], leading to the number of cells $N_{model}^{IC} = c_m^{IC} \mathrm{d}v^I M_m^{IC} M^{IC}$. Additionally, a summation throughout the model domain at each time step is carried out giving $N_{model\,total}^{IC} = \sum N_{model}^{IC}$.

The volume data V_{ges} of the spheroid-growth experiments are divided by the volume of a single cell V_{IC}, assuming full contact between every cell, resulting in the total cancer-cell number $N_{data\,total}^{IC} = V_{ges}/V_{IC}$. Moreover, $N_{model\,total}^{IC}$ is then fitted to $N_{data\,total}^{IC}$ by manually adjusting the proliferation parameters $\mu_{\oplus}^{IN} \propto \mu_{\oplus}^{IN}(\mu_{fast}^{IN}, \mu_{med}^{IN})$, respectively κ^{IC}. Besides the estimated proliferation parameters, as shown in Table 1, a parameter deviation of $\pm 25\%$ is included in Figure 2 illustrating a range for the parameter modification as well as the response of the model.

Monod-type	**Logistic-type**
$\mu_{fast}^{IN} = 1.60 \cdot 10^{-6}\ [1/s]$	
$\mu_{med}^{IN} = 6.42 \cdot 10^{-7}\ [1/s]$	$\kappa^{IC} = 1.33 \cdot 10^{-6}\ [1/s]$

Table 1. Manually fitted parameters of the proliferation descriptions

Conclusions

In this contribution, a continuum-mechanical model for cancer-cell proliferation was introduced, wherein the mass-production term was either described by a Monod-type or a Verhulst-type equation.

Finally, the sum of least squares at the measurement times $\sum (N_{model\,total}^{IC} - N_{data\,total}^{IC})^2$ is calculated revealing the quality between the proliferation descriptions, cf. Table 2. The shown sum of least squares illustrates the better agreement of the data involving the Verhulst-type equation. Therefore, this proliferation description is favourised for further studies. Nevertheless, both proliferation descriptions are in the range of the standard deviation of the experiments.

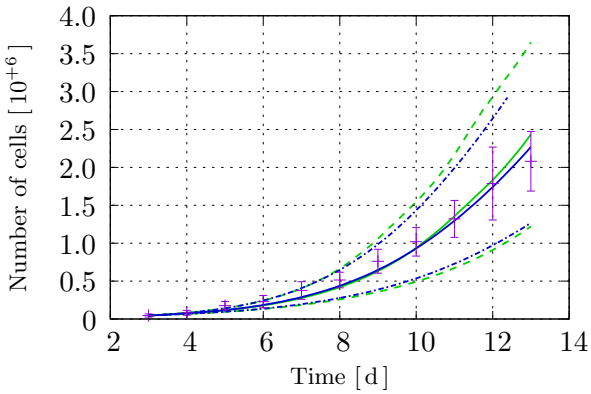

Figure 2. Cancer cells were grown as a spheroid over the time period of 13 days. The data points correspond to the mean ± standard deviation of the calculated number of cells (purple). The simulation results are indicated in green for the Monod-type equation and in blue for the Verhulst-type equation. The dashed lines correspond to a 25% deviation of the estimated parameters. The lung-cancer experiments are performed at the Institute of Cell Biology and Immunology, University of Stuttgart, Germany.

Monod-type	**Logistic-type**
$3.15 \cdot 10^{+4}$	$2.31 \cdot 10^{+4}$

Table 2. Sum of the least squares between the experiments and the continuum-mechanical model applying the Monod-type and the Verhulst-type equation to the mass-production term.

In conclusion, both equations are capable of simulating the experimental data. The Monod-type equation contains more biological aspects, and the Verhulst-type equation offers a simpler description.

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