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The Mechanical Underpinning of Tumour-induced Angiogenesis and Growth

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ABSTRACT

Angiongenic vessel growth is widely acknowledged to be a fundamental process that underpins cancer growth, invasion and metastasis, and it is highly instructive to construct and test reliable mechano-biological models of this process. Whereas previous studies have explored the chemical underpinning of both tumour growth and angiogenesis, here we extend these frameworks significantly to focus on the interplay between angiogenic network evolution and growth-induced solid stresses through a hapto- and mechanotactic stimulus for vessel sprouting, and a mechanics based remodelling process of the microvasculature. The proposed three-dimensional, multiscale *in silico* model for tumour-induced angiogenesis and growth is validated against *in vivo* data from murine mammary carcinomas, specifically focusing on the role of mechanical signals in recapitulating experimental evidence.

Key Words: *cancer mechanics; neo-vascularisation; tumour microenvironment; multiscale model; finite element method*

1. Introduction

Over the past two decades there has been a rapid development of deterministic mathematical and computational models describing cancer behaviour. These span from single scale to multiscale models, based either in continuum, discrete or hybrid methodology approaches. Cancer models that target simulating the dynamics of solid tumour biomechanics can be classified into avascular and vascular tumour growth models, with the reviews [4, 5] providing an exhaustive list of publications in the field. In this paper we propose a novel *in silico* model of tumour-induced angiogenesis and growth. This model is capable of producing high fidelity predictions of the morphology of the tumour microvasculature and its structural characteristics (e.g. endothelial lining, pore-size) and, importantly, it is has been validated against *in vivo* data from murine mammary carcinomas. The novelties of the model include: the introduction of mechano- and haptotaxis in capillary tip elongation; utilisation of a phenomenological description for the elongation speed of sprouts; and development of a constitutive model to describe vessel wall remodelling and structural integrity as a function of mechanical cues. Last but not least, an innovation of the proposed methodology is that it couples, in a partitioned manner, the tumour–host solid mechanics with the fluid mechanics of the capillary–interstitium interaction and the balance of biochemical factors regulating tumour growth and angiogenesis.

2. Methodology

The proposed *in silico* cancer modelling framework consists of four interconnected modules, as shown in Fig. 1: the solid mechanics (Box A), the biochemics (Box B), the microvasculature (Box C), and the fluid mechanics (Box D). This coupled model is solved using finite element (FE) methods using our in-house numerical analysis tool FEB3. Details of the novel aspects of the mathematical model and its computational implementation are summarised next.

We employ a continuum modelling approach to describe tissue solid and fluid mechanics, and biochemical transport. The domain of analysis consists of a spherical tumour (1 mm diameter) embedded in a cuboid (1.7 cm^3) of healthy tissue. The tumour region is initially avascular, with an initial spatially-uniform vascular network seeded in the healthy tissue. This 3D vasculature evolves temporally in response to

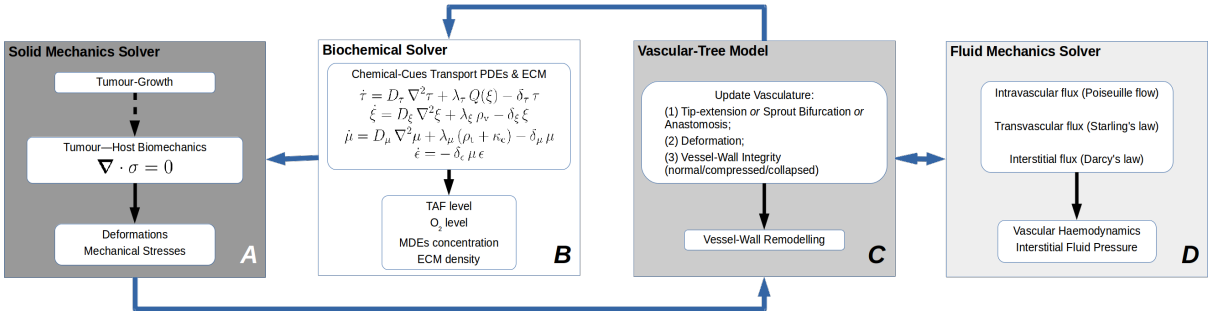

Figure 1: Flow diagram of the coupled multiscale solver illustrating the interaction between the different solvers.

both chemical and mechanical cues, and is described using a discrete description of individual vessel segments, connected via nodal junctions. Throughout, transient analysis is resolved using an explicit time-integration scheme. A set of three coupled equations are solved for the tumour angiogenic growth factor (TAF) concentration, τ, secreted by the cancer cells; the oxygen concentration, ξ, which diffuses from the blood vessels into the extracellular matrix (ECM) where it is metabolised by the cells; the concentration of matrix-degrading enzymes (MDE), μ, which is produced by endothelial cells in the sprouting vasculature, and the tumour cells, and diffuses through the ECM. The local composition of the ECM, ϵ, changes dynamically due to MDEs cleaving the proteins in the matrix. Tumour development is stimulated by the local increase of oxygen in the tissue using a physiologically representative growth expression and tissue biomechanical properties [9]. Boundary and initial conditions on the outer boundary of the tissue domain, and also healthy-tumour interface, are chosen to mimic *in vivo* conditions.

The initial vascular network, seeded within the healthy tissue, has properties (i.e. lumen size, thickness, pore size) obtained from *in vivo* data [6]. The vascular grid is non-conforming to the tissue FE-mesh. The meshes are coupled in the fluid mechanics solver (Box D of Fig. 1), where the steady-state fluid problem is solved [7], and the interstitial fluid pressure (IFP) and the fluid microvascular pressure (MVP) are evaluated. The vascular network evolves in response to both chemical and mechanical stimuli. First of all, the orientation of elongating vascular sprouts is described by the superposition of chemo-, hapto- and mechanotaxis stimuli: $\boldsymbol{e} = k_\tau \nabla\tau - k_\epsilon \nabla\epsilon - k_\mathrm{m}\, \boldsymbol{t}$, where k_τ, k_ϵ, k_m are scalar parameters, and $\boldsymbol{t}$ is the minimum eigenvector of the tissue mechanical stress tensor. Following recent *in vitro* experimental observations [10], we also impose that the tip elongation speed is inversely dependent to the vessel lumen size. Finally, the capillary lumen diameter and wall properties remodel in response to both the wall shear stress (WSS), and also compressions via the accumulated mechanical stresses in the tissue (a vessel collapses and its flow is occluded when the load exerted on its walls exceeds a critical value).

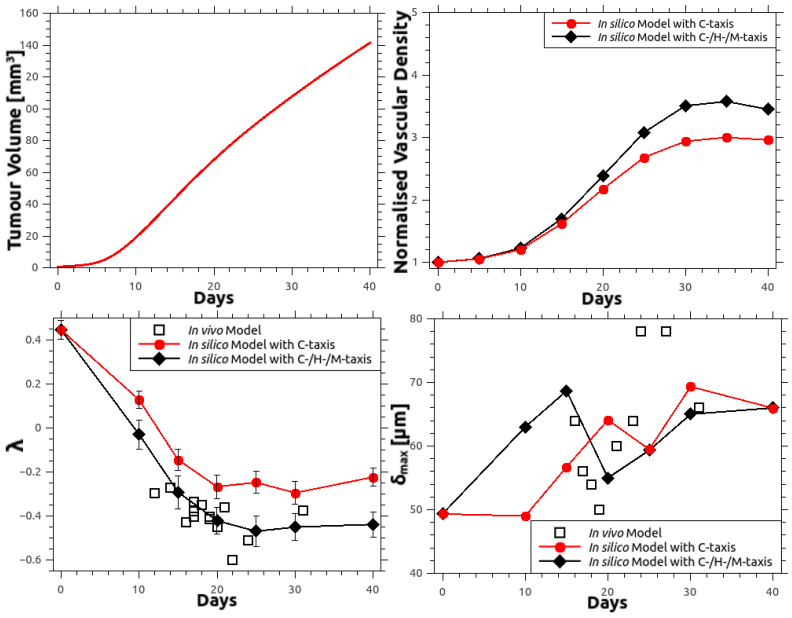

Figure 2: A. Predicted tumour volume as a function of time. B. Predicted vascular density (capillary lumen surface area to tissue volume ratio) normalised against the initial vascular density. C, D. Predictions of the tumour vasculature scaling parameters λ and $\delta_{\max}$ [1], compared with *in vivo* measurements [8].

Predictions of the *in silico* model (with and without mechanical stimuli switched on) are compared against both reported literature observations, and *in vivo* experimental data which characterises tumour growth, vascular extent and fluid flow characteristics in murine mammary carcinomas [8], providing a crucial validation step of these types of computational tumour frameworks.

3. Results

Fig. 2A shows the predicted bulk tumour growth (diameter increase from 1 to 6.5 mm in a month), with Fig. 3 illustrating tumour-induced angiogenesis and size at discrete time points (cancer mass shown as a transparent sphere); here the capillaries are shown as cylindrical tubes scaled to their lumen diameter. From left to right, Fig. 3 shows MVP, mean blood velocity, WSS, and radius respectively. In the rightmost panel, the concentration field of TAF (secreted by the tumour cells) is overlaid with the functional (red) and collapsed (blue) vessels; this collapse occurs due to the high solid stresses around the tumour-healthy tissue interface. The *in silico* cancer model predicts uniform IFP of around 8.5 mm-Hg in the tumour, with a steep decrease in the peri-tumoural region. This result is within the experimentally measured pressure range for tissue-isolated (7.8 ± 3.8 mm-Hg) and subcutaneous (9.1 ± 3.9 mm-Hg) small-size tumours [2]. The predicted maximum interstitial fluid velocity is approximately 0.15 μm/s, which is the correct order of magnitude with respect to experimentally measured values (0.6 ± 0.2 μm/s) [3]. In tumours, normalised vascular density (capillary lumen surface area to tissue volume ratio, normalised against the initial vascular density) is reported to range from 3.3 to 5 [11]. Fig. 2B depicts the temporal change of the normalised vascular density. We compare the model results when vascular sprouting is regulated by chemotaxis only, or in combination with mechano- and haptotaxis. Model predictions in each scenario are within physiological limits. We also adopt the method in [1], where two scaling parameters, λ and $\delta_{\max}$, were introduced to quantify key vascular features in 3D. Here λ is defined as a measure of the distribution of blood vessels in space, and $\delta_{\max}$ measures the distance between a point in the interstitium to the nearest blood vessel. A comparison between model predictions and the *in vivo* data from MCaIV carcinomas is presented in Figs. 2C and 2D. Whereas the simplified chemotaxis model (mechano- and haptotaxis switched off) overestimates λ at all time points, the agreement between model and experiments is excellent when the mechanical features are included. The impact of these features had a less significant effect on $\delta_{\max}$ because tumour growth in the model is not affected by the structure of the newly formed vasculature.

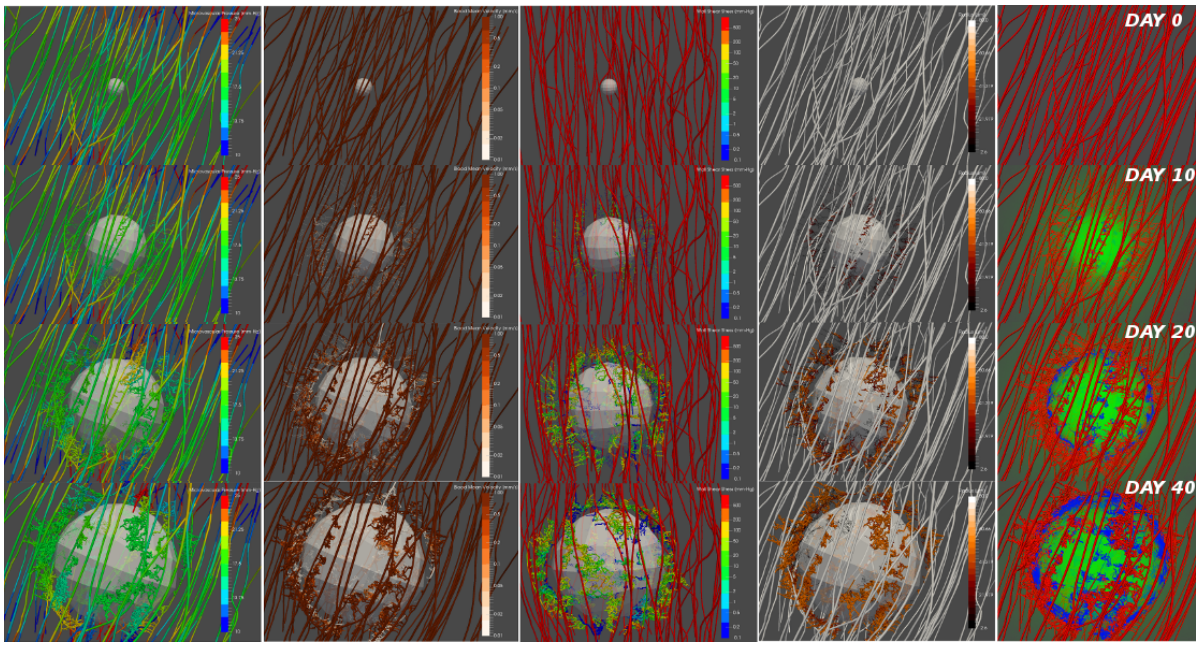

Figure 3: Snapshots of the *in silico* cancer model predictions, illustrating: MVP, velocity, WSS, capillary radius, and TAF distributions together with functional (red)/collapsed (blue) vessels.

4. Conclusions

This paper presents a validated 3D multiscale model of tumour-induced angiogenesis and growth, which incorporates a comprehensive description of the coupling between the tumour mechano-biology and capillary network fluid flows, functionality and growth. Model predictions are validated against experimental measurements of fluid pressures and velocities, and quantification of vascular parameters, and this agreement is strongest when angiogenic behaviours are driven by not only chemo-, but also hapto- and mechanotactic stimuli. Therefore, this study provides strong support for the importance of mechanical factors in influencing tumour vascularisation and development.

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