A Scale Separation Approach Applied to a Mathematical Model of Solid Tumour Growth

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1. Introduction

Cancer is a complex and heterogeneous disease which depends on several phenotypic changes or hallmarks e.g. evasion of growth suppressors, secretion of molecules inducing angiogenesis, replicative immortality [1]. The solid tumour can grow or regress depending on the biological and mechanical factors that occur at different scales: tumour, stroma, cellular and subcellular/molecular scales.

Computational models are a tool that has been largely used to better understand the underlying mechanisms of solid tumours. Several notable approaches are discrete models such as agent-based models, continuous models such as partial differential equations, and hybrid models. Solid tumour models range from macroscopic representations of volumetric growth to the microscopic molecular processes [2].

One important question is how to separate a multiscale model of such diverse phenomena into multiple single-scale models so that each one represents a specific space-time scale. This work presents a theoretical analysis of this problem based on the work proposed by one of the authors in [3] to explore the scale separation of a multiscale tumour growth model being developed in the PRIMAGE project [4].

2. Methods

Initially, a scale is defined in terms of grain, which is the largest value between the lower limit of spatial/temporal resolution allowed by instrumentation, and the smallest/fastest feature of interest. And the extent, which is the smallest value between the upper limit of spatial/temporal resolution and the size of the largest/slowest feature to be observed.

The first step in defining the scale separation of the multiscale model, described in [3], is the definition of the mathematical model that offers the infinite resolution representation of the multiscale model under development (Eq. 1).

$$
\begin{cases}
\pi^{*}_{\gamma_k}(k(X), T_l, t) = \pi_{\gamma_k}\left(I_k, \alpha_k, \tau_k, S_1, \dots, S_J, t\right) \cdot \pi^{treat}_{\gamma_k}(T_l) \\
r_i^{dV_X}(X,t) = \dfrac{dc_i^{dV_X}\left(X, S_1, \dots, S_J, t\right)}{dt} \\
\dot{S}_j(X,t) = \sum_{k}^{N \in dV_X} \chi_k^j(I_k, \alpha_k, \gamma_k, \tau_k, t) + \sum_{k}^{N \in dV_X} \sigma_k^j(I_k, \alpha_k, \gamma_k, \tau_k, t) \\
r_i^{dV_X}(X,t) = f_p^{i,a}(X,t) - f_d^{i,a}(X,t) = \dfrac{dC_i^{dV_X}(X,t)}{dt} \\
\dfrac{\partial C_i^{dV_X}(X,t)}{\partial t} + \nabla \cdot \left(C_i^{dV_X}(X,t)\dfrac{\partial u(X,t)}{\partial t}\right) = r_i^{dV_X} \\
\dfrac{\partial V}{\partial t} = k^{ia}\left(\dfrac{\partial C^V}{\partial t}\right) = k^{ia}\left(\dfrac{\partial C_s^V}{\partial t} + \dfrac{\partial C_n^V}{\partial t}\right),
\end{cases}
\tag{1}
$$

in which, X is a generic point within the tumour and t is the time. $\pi^{*}_{\gamma_k}$ represents the probability that a cell k in an untreated tumour changes its internal state γ_k, and is a function of the cell's type I_k, its differentiation level α_k, the telomerase state of cell k (τ_k). and the local concentration of the chemical species ($\dot{S}_j$), that is supplied to the tumour volume at rate χ_k^j and consumed by the tumour cells at rate σ_k^j. T_l represents the treatment and l is the treatment type. The proliferation rate of cells of type i located within the infinitesimal volume dV_X is represented by $r_i^{dV_X(X,t)}$ and the concentration of cells of type i is C_i. Finally, the volume of the whole tumour is the sum of the cellular and the extra-cellular matrix volume for every cell type i, in a differentiation state α.

Following that, we divide the spatial domain into three levels using hybrid numerical approaches (Fig. 1). The dimensional analysis shown in Fig 1 represents the temporal and spatial scales in the context of the neuroblastoma model. The hypothetical infinite resolution model would span nine orders of magnitude both in time and space. This model is currently intractable, so a multiscale model is necessary.

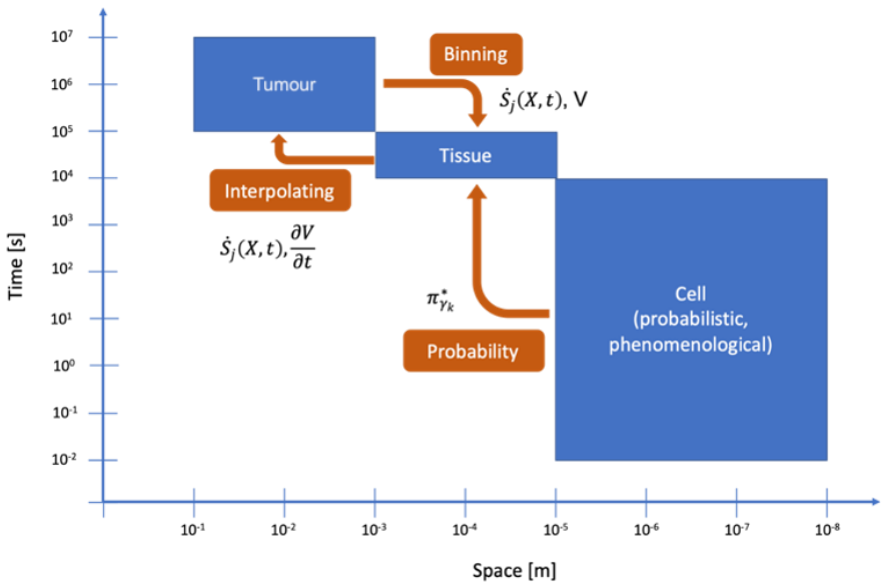

Figure 1 *Scale separation map for multiscale solid tumour growth model.*

A Finite Element Model (FEM) is proposed to represent the whole tumour using patient-specific images and an Agent-Based Model (ABM) is proposed to describe cell behaviour at the tissue scale. The latter receives information about the availability of nutrients from the former via particularisation and sends information about cell proliferation/apoptosis (considering probabilistic information from cell-scale model) that reflects in changes in volume via interpolation.

Every paper that describes a multiscale model should provide justification for its scale separation based on the resolution of the experimental methods available to inform the model and the computational power available for its solution.

References

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