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Effect of particularisation size on the accuracy and efficiency of a multiscale tumours' growth model

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Abstract

In silico, medicine models are frequently used to represent a phenomenon across multiples space–time scales. Most of these multiscale models require impracticable execution times to be solved, even using high performance computing systems, because typically each representative volume element in the upper scale model is coupled to an instance of the lower scale model; this causes a combinatory explosion of the computational cost, which increases exponentially as the number of scales to be modelled increases. To attenuate this problem, it is a common practice to interpose between the two models a particularisation operator, which maps the upper-scale model results into a smaller number of lower-scale models, and an operator, which maps the fewer results of the lower-scale models on the whole space–time homogenisation domain of upper-scale model. The aim of this study is to explore what is the simplest particularisation / homogenisation scheme that can couple a model aimed to predict the growth of a whole solid tumour (neuroblastoma) to a tissue-scale model of the cell-tissue biology with an acceptable approximation error and a viable computational cost. Using an idealised initial dataset with spatial gradients representative of those of real neuroblastomas, but small enough to be solved without any particularisation, we determined the approximation error and the computational cost of a very simple particularisation strategy based on binning. We found that even such simple algorithm can significantly reduce the computational cost with negligible approximation errors.

KEYWORDS

homogenisation, in-silico, modelling, multiscale, oncology, particularisation

1 | INTRODUCTION

In most biological problems, biological entities operating at a spatial scale of some microns (e.g., cells) produce clinically relevant effects that manifest at a much larger spatial scale (e.g., tissue, organ, organism). Same applies for the temporal scale: chemical reactions taking place in a few milliseconds may produce effects observable over years. For

example, with reference to the modelling of solid tumours growth, the space–time scales to span are 10^{-8} to 10^{-1} m, and 10^{-2} to 10^{7} s.[1] Hereinafter, we define range of a model, the largest portion of space or time the model accounts for, and grain, the smallest portion of it.[2] The grain is frequently referred to also as the representative volume element (RVE). A neuroblastoma can reach volumes as large as 4,188,790 mm^3 (a sphere of 20 cm of diameter). The representative volume element (RVE) of the tissue-scale model is equal to the average size of tumour cell ($\approx$ 10 μm). Current models can account for the interactions of around 1 million cells (which correspond to a range of ≈ 1 mm^3) over 2 weeks in roughly 2 min of computations, using a single graphic processing unit (GPU). Even in the unrealistic assumption that the parallelisation of such model scales linearly, to solve the tissue-scale model over the entire tumour volume would thus require 111,7011 GPU-hour on a large GPGPU cluster to simulate a full four-months chemotherapy cycle. Splitting the problem into two single-scale models does not significantly change the computational cost: the whole tumour model would need an RVE of 1–2 mm^3, so we would need to solve millions of tissue-scale models, one for each RVE of the tumour-scale model. However, if we can interpose between the two single-scale models particularisation / homogenisation operators, the number of tissue-scale models to run can be reduced. This comes at the price of introducing some additional approximation error in the solution. It is also important that this operator is as simple as possible, to reduce the computational overhead that the multiscale orchestration imposes.

The simplest particularisation strategy is based on binning. In meteorology, the pairwise homogenisation algorithm uses statistical analysis to dynamically define the bins.[3] In fracture mechanics, binning-based particularisation is implemented by placing bins at the Gauss quadrature points.[4] Binning particularisation is also used successfully in the reconstruction of genomes,[5] but to authors' knowledge, it has never been proposed for computational oncology problems. There are of course more sophisticated particularisation methods described in the literature. In fracture mechanics are common hybrid multiscale methods combining homogenisation and domain decomposition approaches for example,[6] in the field of composite materials, it is common the use of the theory of asymptotic particularisation of periodic media,[7] which can be formulated with guaranteed accuracy.[8] Similar methods were also used to homogenise the properties of solid tumours[9]; however, two key assumptions (periodic microstructure, and strong separation of scales) are hardly met in this type of tissues. Problems of mass transport by diffusion within composite materials have been homogenised assuming that the mass release curves for the detailed microstructural and continuum models.[10] De la Cruz et al. propose a quite elegant hybrid method to homogenise continuum and cell-scales in tumour growth multiscale model.[11] However, their purpose is not that of reduce the computational cost of the multiscale model. On the contrary, the method they propose introduces a non-negligible overhead to homogenise the boundary conditions between the two scales.

The aim of this study is to evaluate the error caused by a specific implementation of the particularisation / homogenisation process based on binning, as a function of the number of bins, in a multiscale model of growth for neuroblastoma tumours. The model uses the particularisation / homogenisation process to link a whole-tumour scale continuum model that calculates oxygen diffusion and the biomechanical interaction of the growth process, with tissue-scale agent-based models that simulate the activation, replication, differentiation, and death of the various cellular populations involved with this specific tumour growth. As the overall computational cost of the model's solution depends on the number of tissue-scale models we need to run at each time step, which is equal to the number of bins used for the organ-to-tissue particularisation, there is a trade-off between the level of detail of the particularisation and the computational cost to solve the multiscale model.

2 | MATERIALS AND METHODS

2.1 | A brief overview of the biological problem and its idealisation

One of the aims of the PRIMAGE project[12] is the development of digital twins (patient-specific models) that can predict the growth of a neuroblastoma (a type of solid tumour) when left untreated or when treated with different chemotherapies. Living cells can replicate through a process called mitosis, where a single cell divides in two. Healthy human cells have a number of molecular mechanisms that limit the rate of replication, and the number of times a cell can replicate during its life. Due to mutation, some cells might lose these limitation mechanisms and start replicating indefinitely. This produces a solid tumour, which is a tissue mass composed of tumour cells and of the extracellular matrix they secrete. As the tumour grows, it compresses the surrounding tissues and organs, compromising their functions and eventually killing the patient. There are various things that may slow down the growth of a neuroblastoma, but the PRIMAGE model focuses on three: the transport to and from the surrounding vascular network that brings oxygen and

other nutrients to the growing number of cells and removes from them their metabolic waste substances; the biomechanics of volumetric expansion of the tumour geometry due to the cells' replication; how the cells respond to the specific chemotherapy. Oxygen diffusion in the tumour mass is regulated by the cellularity (the volumetric ratio between cells and matrix) and the vascularity, the density of capillary vessels that form within the tumour as it grows. Chemotherapy may reduce the replication rate and increase the death rate of tumour cells. How effective a specific chemotherapy cocktail is in doing this depends on molecular make-up of the mutated tumour cells.

The PRIMAGE model predicts the change in geometry of the tumour over time depending on the treatment, as a function the following input set: geometry, cellularity and vascularity at the beginning of the treatment, which are quantified with Magnetic Resonance Imaging; and several molecular biomarkers obtained by analysis the tumour biopsy. The mathematical model is built assuming that each cell change states is a probability function $\pi_{\gamma k}$ (Equation 1) that depends on the type of cell I_k, its differentiation level α_k, its telomerase1 state τ_k, and the concentration biochemical species S_i at the cell location. Equation (2) represents the cumulative probability of internal state change for cell k as a function of the treatment type.

$$\pi_{\gamma_k}(k(X), t) = \pi_{\gamma_k}\left(I_k, \alpha_k, \tau_k, S_1, S_2, ..., S_j, t\right) \tag{1}$$

$$\dot{S}_j(X, t) = \sum_{k}^{N \in dV_x} x_k^j(I_k, \alpha_k, \gamma_k, \tau_k, t) + \sum_{k}^{N \in dV_x} x_k^j(I_k, \alpha_k, \gamma_k, \tau_k, t) \tag{2}$$

The changes over space and time of the concentrations S_i can be formulated as a diffusion–reaction equation. The density of the various cell types in space as a function of the replication/death events and of the biomechanical deformation of the tissue can be formulated in terms of mass conservation equations. If we assume the cellularity does not change as much as the tumour grows, the change of volume of the tumour over space and time can then be formulated as a partial differential equation function of the changes in the local concentration of cells. The complete mathematical treatment can be found in reference 1.

Scale separation analysis[1] suggested to decompose the problem into three single-scale models, properly orchestrated. The cell model, which computes Equation (1), needs to be run only once at the outset. Thus, the orchestration is limited to the coupling of the tumour model with the tissue model. With respect to the results of the scale separation analysis, the final implementation of the multiscale model presents some differences, dictated by computational constraints. The tumour model solves the diffusion–reaction equations for the initial conditions dictated by the imaging data using a finite element scheme. A tissue model is then run for each finite element: the tissue models simulate the evolution of the cells in the compartment for the following 14 days. This is the longest time that in the untreated model predicts a change in volume that the tumour model can handle without the need for remeshing. With the updated values of volume, cellularity, and vascularity for each finite element the tumour model simulates first the volumetric expansion. The resulting geometry is the re-meshed, and then the diffusion–reaction simulation is run again with the new values of vascularity and cellularity. The tissue scale models are executed again to simulate another 14 days, and so forth until the whole chemotherapy cycle (typically 16 weeks) is simulated.

2.2 | Implementation details

The current version of the PRIMAGE multiscale model requires the coupling of two component models. The first component model is a finite element model developed by the University of Zaragoza (ES) that solves the diffusion–reaction equations and the biomechanics of the volumetric expansion equations. The volume of the whole tumour at time zero is decomposed into a finite element mesh of 4-node linear tetrahedrons. The average element size is an order of 10^{-2} mm. The tumour-scale model is entirely deterministic; if the model is run twice with the same input, it will predict the same output. The tumour-scale model is solved using a commercial general-purpose solver (Ansys v19.5, Ansys Corp, USA), which runs on CPU cores.

The second component model is an agent-based model (ABM) developed by the University of Sheffield (UK). In the ABM tissue-scale model each relevant cellular type is modelled as an autonomous agent, whereas the diffusion–reaction of the chemical species in the compartment are described through a system of differential equations solved with a finite difference scheme. The growth of the tumour is described by a set of rules that regulate when each cell moves, replicates or dies. The tissue-scale model is stochastic in nature, so the same input will not produce the same

output. The ABM model is run using the Flame GPU framework[13] also developed by the University of Sheffield, and distributed in Open Source.[14] The ABM runs predominantly on GPU cores.

The reference volume element (RVE) for the ABM is a cube volume shrunken based on the initial parameters of the model (e.g., element volume, cellularity and cell density). We assume that the ABM RVE is fully contained inside the tetrahedron of the tumour-scale model and positioned at its centroid (Figure 1). The two models are coupled by an orchestration software layer that handles the data flow, according to Figure 2. Between the two models there is a relation process, described in the following section, that handles the scale transformations.

In principle, we should run a tissue-scale model for each finite element in the tumour-scale model. But considering that real tumours models could have millions of elements, this is not possible. Thus, a relation model is added to the orchestration to handle the particularisation / homogenisation process.

The multiscale model was run on PLGrid2 Prometheus HPC cluster3, managed by Cyfronet, composed of Intel Xeon E5-2680 CPUs and 144 Nvidia Tesla K40 XL GPGPUs. The cluster uses Linux CentOS7 as an operating system and the SLURM scheduling system.

2.3 | Data

The whole study was conducted on an idealised tumour model, small enough to allow a solution without any particularisation with the computational resources available. The idealised tumour model assumes the cancer to be a

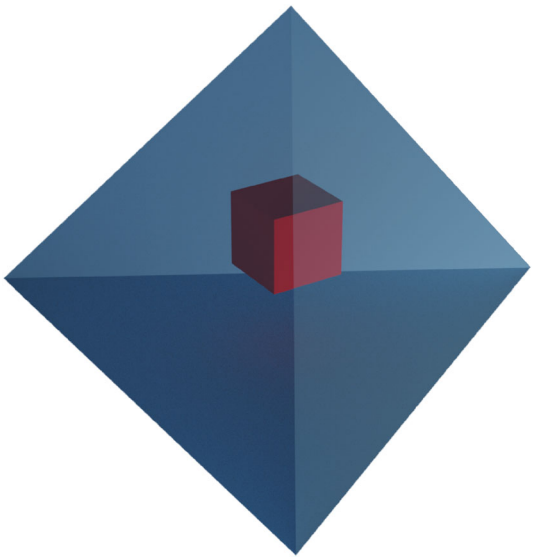

FIGURE 1 Cubic-shaped RVE for the ABM (red) for a tetrahedron mesh element.

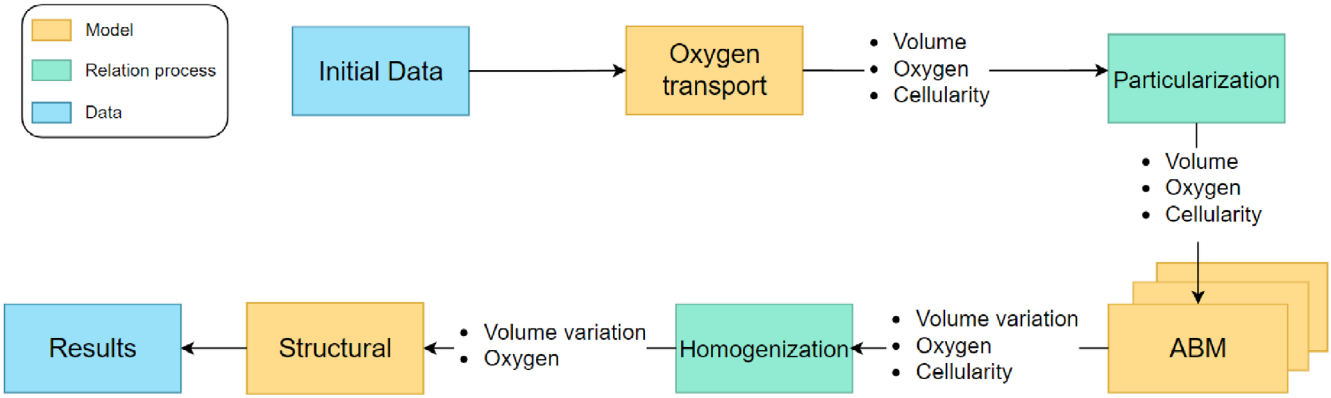

FIGURE 2 Topology of the orchestration software layer

spherical solid tumour of 5 mm in diameter, an initial volume of 524 mm^3, which is meshed with 4448 finite elements. Vascularity is represented in the model in term of oxygen concentration. Oxygen concentration is dimensionless because is normalised with maximum oxygenation levels according to literature; the initial oxygen concentration is assumed to be 1 at the outer skins and 0 at the centre with linear variation along the radius. This produces an initial gradient that equal or greater than the one we would expect in real tumour data. The model assumed the cellularity (ratio between cancer cells volume and the total cancer volume) to remain constant over the entire simulation. The multiscale model is run to reproduce the growth of this idealised tumour for a period of 2 weeks, without any treatment. The treatment would always slow down the growth, so the no-treatment option is the most critical for the particularisation algorithm. While, ideally, we should calculate the particularisation error over the full duration of the chemotherapy cycle, as the error propagates, the re-meshing required after 14 days would make impossible a reliable evaluation of the particularisation error.

2.4 | The particularisation/homogenisation relation model

Between the two component models, there is a relation model that has the function of gathering all the data necessary to write the inputs of the next model and doing the transformations requested for making the scale change, here named as particularisation and homogenisation (Figure 2).

Those processes complement one with each other; the particularisation gets the outputs from the macro-scale and groups the elements of the mesh in sets called bins. The homogenisation gets the outputs of the micro-scale and estimates them to the macro-scale.

The binning process algorithm orders the elements by one variable and groups them in sets of the same size (or the closest possible to it). The biggest value of each bin is selected to run the tissue model.

The homogenisation gathers all the results obtained by the tissue model and estimates the values (oxygen and volume) for the elements that were not run, using a linear approach on the order the elements were sorted at the particularisation, resulting in a set of data by elements. However, the last component model requires that the oxygen input values are written per each node of the FE and not per element. This is done by considering the concentration of oxygen in each node as a simple average of the oxygen value of all the elements that are connected to the node.

The particularisation algorithm can operate on one variable at a time. In our case, the coupled models exchange two quantities, the oxygen concentration and the change in volume. A preliminary investigation confirmed that the spatiotemporal gradients of oxygen concentration were much greater than those of the changes in volume; thus, the particularisation algorithm was run on the oxygen concentration. However, we also monitored the error induced in the other variable. On the contrary, we did not explore the effect of particularisation on cellularity, because in this implementation it is assumed to remain constant.

2.5 | The validation study

We first run the whole multiscale model without any particularisation (number of bins = number of finite elements). At the end of the simulation, we recorded for each finite element of the tumour-scale model the oxygen concentration, and the change in volume (tumour growth).

We then repeated the simulation several times, each time progressively reducing the number of bins. Since the tissue-scale model is inherently stochastic, if we rerun the model, we would see differences not only due to the number of bins we use but also due to the stochasticity. In order to separate these two sources of variation, in each of these reruns, we did not run again the tissue-scale model, but we simply used the full-resolutions results obtained with the initial simulation. This way, we were certain that the only difference between repeated simulations would be due to the level of particularisation.

To describe the average error caused by each level of particularisation for each coupled variable (oxygen concentration, and changes in volume), we used the root mean square error (RMSE). The RMSE was plotted as a function of the percentage of tumour-scale elements that were simulated at the tissue-scale level (hereinafter referred as granularity, defined as the opposite of particularisation).

Considering the primary reason for particularisation is to reduce the duration and cost of the simulation, we also plotted the RMSE as a function of the wall-clock solution time, and of the total number of core-hours (under the assumption that CPU and GPU cores had the same weight).

3 | RESULTS

Two cases of particularisation were tested, particularising by oxygen concentration and by the variation of volume. In each test, several executions were run only changing the size of the particularisation (number of bins) and comparing to the value obtained without doing particularisation and homogenisation (full resolution result)for calculating the root mean square error (RMSE), divided by the full resolution result to normalise. The percentage granularity represents the fraction of finite elements that had the outputs estimated by the tissue-scale model, that is, the percentage of granularity is equal to one minus the percentage of elements particularised. Therefore, the smaller is the percentage granularity, the closer it is to the case without particularisation (which has 0% granularity).

The percentage of RMSE error is plotted versus the percentage of granularity for both variables where the particularisation variable is the oxygen concentration (Figure 3), or the variation of volume (Figure 4).

The particularisation by oxygen resulted to be much more accurate. While the particularisation by volume at 95% granularity cause errors of 60% on the variation of volume and 7% in the oxygen concentration, the particularisation by oxygen at 95% granularity caused errors below 1% for both variables (specifically .4% for the variation of volume, the primary output of the model).

The computational cost for the whole orchestration is reported in Figure 5 in terms of core-time and memory allocation for the case of particularisation by oxygen. While the simulation of 2 weeks of growth for a small, idealised tumour used in this study requires 104 core-hours and over 14 GB of allocated memory to be solved on the in the Prometheus cluster without particularisation, an 95% granularity model can be solved with only 5 core-hours and 700 MB of memory. This means that the largest tumour would require 400,000 core-hours to simulate the whole 4 months of chemotherapy for each of the treatments being tested. Considering that current pre-exascale European supercomputers like Leonardo being installed at the CINECA Italian HPC centre has 14,000 GPU cores that are nearly 10 times faster than the one we used in this study, a simulation could be done in 8–10 h with a third of the core available.

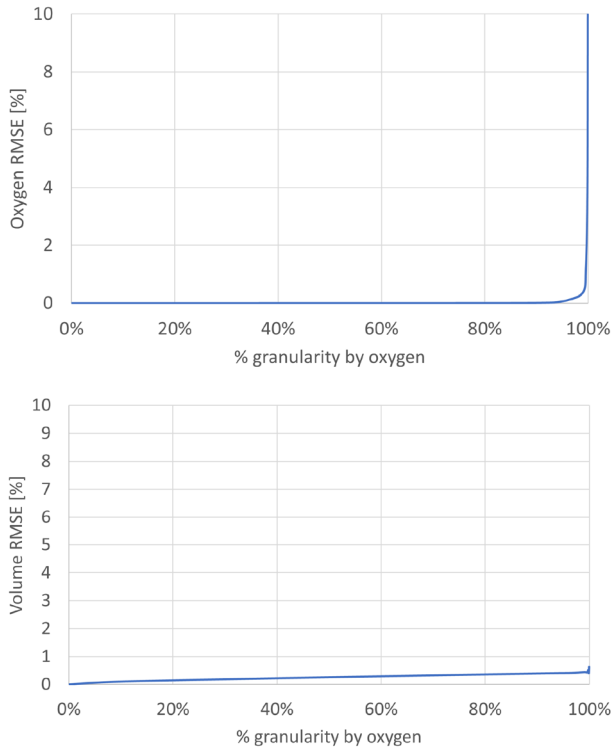

FIGURE 3 Error of the results for the oxygen concentration and volume variation with particularisation by oxygen.

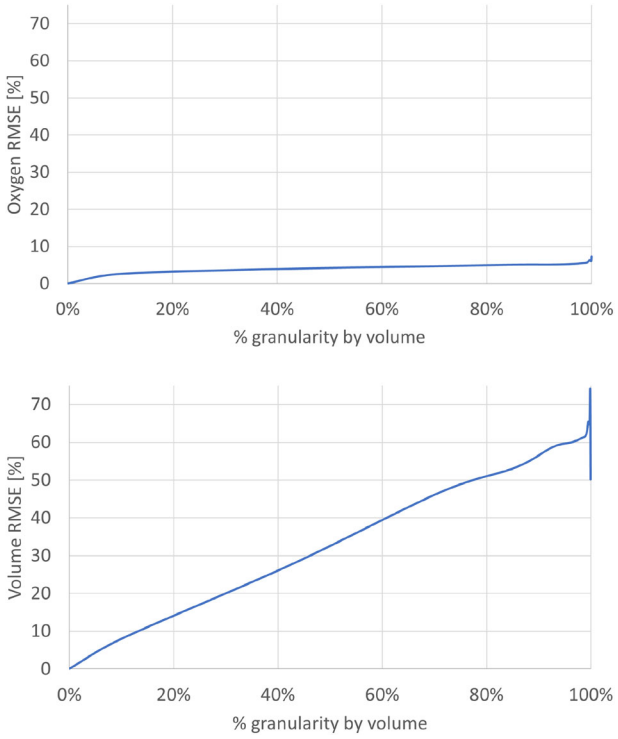

FIGURE 4 Error of the results for the oxygen concentration and volume variation with particularisation by volume.

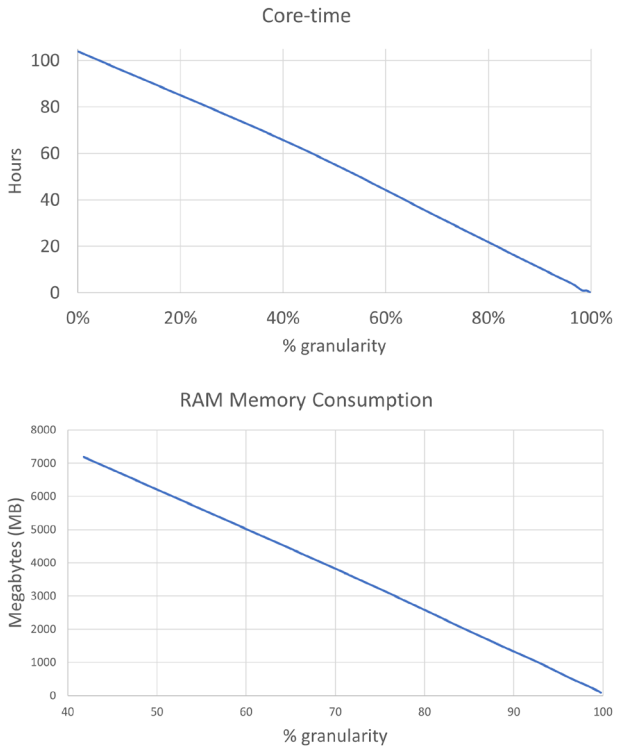

FIGURE 5 Core-time and RAM memory consumption varying the granularity of the particularisation.

4 | DISCUSSION

The aim of this study was to evaluate the error caused by a specific implementation of the particularisation / homogenisation process based on binning, as a function of the number of bins, in a multiscale model of growth for neuroblastoma tumours.

As expected, the binning-based particularisation operator introduced approximation errors that grew with the granularity (number of bins) used in the particularisation, while the computational cost showed an inverse linear correlation with the granularity. Thus, the question is reduced to whether the errors caused by significant granularity (e.g., >90%) introduction approximation errors that are considered acceptable.

In both cases of particularisation, as expected, the error tends to zero when the granularity tends to 0% because fewer values are being estimated (Figures 3 and 4). A particularisation by oxygen concentration with less than 1% of elements sampled (99% of granularity) causes a particularisation error of less than 1% for both oxygen concentration and change in volume. The particularisation by the change of volume is less effective, causing a particularisation error for the oxygen higher than 1% in most of executions and the volume error significantly increases when the granularity is not close to zero.

The core-time consumption graph shows that the impact of the particularisation on the performance is linear and the same occurs to the memory consumption. This occurs because the number of bins determines the number of executions of the tissue model, which is the most computer-demanding part of the orchestration.

This brings us to conclude that, for this problem, a particularisation by binning, while the simplest possible strategy appears to be adequate. In particular, the particularisation by binning of the oxygen concentration cause approximation errors of less than 1% over a 2-week simulation. Considering that the minimal clinically important difference in evaluating a solid tumour treatment is a reduction of at least 35% of the tumour volume,[15] even assuming a full accumulation of the error for a 4-month simulation would still be well below 5%, which can be considered acceptable for the application at hand.

The computer modelling of neuroblastoma growth has received attention in the literature, (e.g.,[16,17]), but most models investigate the problem at a single scale. On the contrary, there very little literature to compare to for multiscale modelling of neuroblastomas. In authors' knowledge the only other work[18] has very different aims, and use no particularisation strategy because they explore only five possible cellular configurations. If we broaden our research to solid tumours in general, probably the closest work is that done by the CHIC project led by Prof Stamatakos on the modelling of a brain tumour, glioblastoma.[19,20] The project used as orchestration software the precursor of that used in this study,[21] but used no particularisation strategy. Other authors proposed for similar problems single-scale models coupling the cellular replication simulated with a cellular automata with the diffusion–reaction problem simulated with a Lattice-Boltzmann scheme.[22] While elegant, this approach, in the paper used to model 1 mm^3 of tumour, is impractical to model tumours that can grow as large as some 10 cm of size.

The main limit of this study is the use of an idealised tumour model. A real-world tumour would be different from this idealised one, for the sheer size, that might be much larger in some cases. However, in term of oxygen gradients, the one we assumed in the idealised tumour model are close to the highest observed in real tumours. A larger size would increase the absolute values of the computational costs but would not change the conclusions on the particularisation errors, which largely depend on such gradient. So, again, the conclusions reached here should remain valid for real-world tumours. Nevertheless, we will repeat a particularisation convergence test for each of the cases used in the future validation studies, in order to confirm that the particularisation error changes asymptotically as the granularity is decreased. Another limit is that in the current implementation the cellularity is assumed to remain constant. This should change in the final implementation, and at that point, it will be worth estimating the particularisation error also for that variable. But again, given its spatiotemporal gradients are expected to be much lower than those of the oxygen concentration, we expect comparable or lower errors.

In conclusion, the use of homogenisation based on a binning strategy in a multiscale model of solid tumour growth can reduce the computational cost by 90% or more, while causing a particularisation error of less than 1%.

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CONFLICT OF INTEREST

The authors declare that they do not have any financial or personal relationships with other people or organisations that could have inappropriately influenced this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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