The Trap of 2D in Artificial Models of Tumours: The Case for 3D In-silico Simulations

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Keywords: Agent-based Models, In-silico Modelling, Bio-oncology, Cancer, Simulations.

Abstract: Artificial modelling of tumours can provide insights in cancer biology and offer a powerful complement to laboratory research. A common approach is to simulate tumour growth in a two-dimensional environment and to then generalize results to a three-dimensional one. Literature suggests this strategy fails to adequately capture the underlying biology and may provide misleading results. To establish whether 2D models may form a viable alternative to 3D ones, we developed a model comprising cancer cell growth and proliferation and soluble diffusion to replicate experiments previously performed in a laboratory. We made use of established parametrization techniques to configure our simulations and novel error estimation strategies to evaluate them. Our results suggest that the same simulation in 2D and 3D yields significantly different results. Further, that the cause of this discrepancy lies in the spatial geometry of 2D simulations which does not allow for the formation of hypoxic regions in the tumour mass. We conclude with a recommendation that due to the limitations of 2D simulations, and the negligible difference in cost between the two approaches, 3D simulations should be employed over 2D ones.

1 INTRODUCTION

Artificial modelling of tumour development is a growing discipline in the field of oncology. Widespread availability of powerful computer clusters and cloud computing resources mean that scenarios comprising large sections of tissue and high number of cells can be easily simulated in reduced amounts of time. The results of these investigations can be used to inform research and promote either further iterations of the in-silico process or in-vivo or in-vitro laboratory experiments.

In-silico simulations offer several advantages as precursors or complements to laboratory wetware research. They allow to rapidly explore multiple 'what-if' scenarios, simulating weeks if not months of tumour growth in the space of hours. They further allow a high resolution of measurements and observations, with properties of individual cells being observable. And finally, they allow to investigate 'causation vs correlation' problems in instances where multiple phenomena could be responsible for a behavior of the tumour mass. This latter is particularly important when devising new therapies, as it is essential that the target phenomenon is actually the one driving the behavior we wish to suppress.

The two most common approaches to cancer modelling are agent-based models and continuous simulations. In the former, agents of different classes are used to represent different cells or group of cells. Each agent class is assigned a set of rules that governs its evolution and interaction with the environment and other cells. In the latter, partial differential equations are used to describe changes in concentration of cells at different positions. These are then solved to observe the evolution of the tumour mass and adjacent tissues in time.

Both approaches require a process of spatial discretization, where the section of tissue being investigated is fit to a structure such as a grid or mesh. For agent-based models, this is so that each position may be occupied by one or more agents. Whereas for continuous systems the solution to the equations will determine the concentration of cells at each position. The most simple example of such discretization involves a Cartesian coordinate system, where the geometry of the grid is consistent across the space and each position's volume or area is constant. More advanced techniques involve meshes with positions of different sizes or shapes, which allows for varying

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Panada, D. and Parsia, B.
The Trap of 2D in Artificial Models of Tumours: The Case for 3D In-silico Simulations.
DOI: 10.5220/0010517702390247
In *Proceedings of the 11th International Conference on Simulation and Modeling Methodologies, Technologies and Applications (SIMULTECH 2021)*, pages 239-247
ISBN: 978-989-758-528-9

levels of resolution across the environment.

A decision that has to be made early in the design process is whether the spatial discretization will produce a two dimensional (2D) or a three dimensional (3D) environment. The case for 2D being that it closely resembles cancer growth in a Petri dish, a commonly adopted approach in laboratories, whereas 3D would allow to more closely mimic tumour growth in living tissues.

It has been suggested that advantages of 3D modelling over 2D include better capturing of oncogene activation (Pickl and Ries, 2009), protein expression and drug sensitivity (Melissaridou et al., 2019; Imamura et al., 2015; Lv et al., 2017) as well as more realistic biochemical and biomechanical environments (Duval et al., 2017) and a better translation of pathophysiological features of the tumour environment (Hoarau-Véchot et al., 2018). Finally, 3D models have also been suggested to better capture intercellular signalling pathways. (Riedl et al., 2017)

An initial survey of the literature reveals a considerable number of publications relying on 2D discretization strategies to obtain insights in tumour biology. These include, among others, studies of blood vessel development in response to angiogenic stimuli (Gabhann et al.,), response to chemotherapy (Sinek et al., 2004) and tumour oxygenation (Skeldon et al., 2012). Additional searches for publications in the field of tumour modelling revealed a large corpus of simulations using a 2D environment. (Zhang et al., 2011; Turner and Sherratt, 2002; Sun et al., 2012; Anderson and Chaplain, 1998; Cai et al., 2011) In cases where 3D was chosen an approach (Olsen and Siegelmann, 2013; Shirinifard et al., 2009; Cai et al., 2016), it is not explained why this was decided for rather than opting for a 2D approach.

Previous related work (St et al., 2005) highlighted differences in simulation performance between 2D and 3D, but did not make an assessment regarding the suitability or unsuitability of either.

Many studies using 2D models do not address the implications and potential limitations of modelling in 2D over 3D. Effects on the spatial distribution of agents, evolution of the tumour mass and soluble diffusion are not addressed, nor is there any attempt, practical of theoretical, at mapping results back to a 3D environment. Finally, it is often not clear how decisions regarding the effective size of a grid position or number of biological cells represented by an agent were taken. While these are model artifacts and properties of the simulation, changes in values could affect the model's output and support or invalidate a thesis.

With these items not addressed and the wealth of literature advocating 3D over 2D, and a substantial corpus of literature opting for both 2D and 3D approaches, we wish to investigate whether it is the case that 2D may offer a cheaper and accurate alternative to 3D or if simulations should on the other hand be preferably or exclusively performed in three dimensions.

The rest of the paper is structured as follows. In our *Materials and methods* section we present our model setup, parametrization strategy and our approach to mapping values from a 3D to a 2D environment. In our *Results* section we present our experimental findings for the various simulations in 2D and 3D, alongside measurements regarding tumour properties such as oxygenation levels, etc. Finally, in the *Discussion* we draw a conclusion with regards to whether 2D form an adequate approach to in-silico investigations or if 3D should be preferably or necessarily employed.

We implemented a simple agent-based model with continuous elements to include diffusion of solubles. Key phenomena accounted for include cellular growth and proliferation, blood vessel development in response to secretion of vascular endothelial growth factors (VEGF) and hypoxia and spatial heterogeneity with regards to oxygen concentration.

We believe that if, despite the simplicity of our model, issues in the 3D to 2D translation still manifest then these would also be present in more complex models. Adding more biology would therefore only make these worse. In summary, the simplicity of our model allows us to explore the effects of 3D to 2D mapping of simulations while minimizing additional work needed to implement more complex behaviours and decide for values in models with a higher amount of parameters.

Our initial setup in 3D was derived from starting conditions reported in medical literature. A translation to 2D was then derived from this, and simulations were run in 3D and 2D. Finally, resulting growth curves were compared to those reported in medical publications to determine whether any difference in error rates were significant. Where possible, parameter values were obtained from literature. Where this was not possible, either because specific values or unknown or because contrasting values are published, hyper-parameter tuning techniques such as grid search (Rios et al., 2013) and random search (Bergstra JAMESBERGSTRA and Yoshua Bengio YOSHUABENGIO, 2012) were employed to explore a suitable search-space.

1.1 Model Overview

We now provide a high-level overview of our model, including key dynamics and properties of agents.

1.1.1 Spatial Discretization

Space is discretized as a Cartesian system. Each position in the grid has its own concentration of solubles (Eg: oxygen) and can host a certain amount of agents. In the 2D model coordinates are identified by pairs of values (Eg: *(2,4)*), in 3D by triplets (Eg: *(2,4,6)*).

1.1.2 Temporal Discretization

Time is advanced in discrete steps of two hour. This corresponds to the length of the shortest stage of the cell life-cycle: Mitosis. At each epoch, soluble concentrations at each position are updated and so is the state of each agent. While in theory each agent is updated simultaneously, this is practically not possible and an order of execution needs to be specified. To avoid systematic bias due to certain agents being always updated first, the scheduling order is randomized at the start of each epoch.

1.1.3 Cell Life-cycle

Our model includes two classes of cells: Cancer cells and endothelial cells. The latter will be discussed in the section dedicated to angiogenesis, whereas here we will be explaining the former.

The main concept behind cancer cells is that of uncontrolled proliferation. Given a sufficient oxygen concentration, cancer cells will keep growing and dividing until a physical constraint owing to their surrounding being saturated occurs. To account for various factors that may delay the division of individual cells, a probability value is set for cells to transition from Growth I (G1) into Synthesis. Upon completing G1, a cancer cell transitions into Synthesis with a given probability which is set as a simulation parameter. If the cell does not transition into Synthesis, it will attempt to do so at the following epoch with the same probability until it does. Once a cell progresses into Synthesis, it will proceed to completing the cell life-cycle and then divide into two daughter cells. The only exception would be if its surrounding environment is saturated, where then it would not be able to further divide.

A cancer cell may be Active, Quiescent or Dead. Active cells are growing and proliferating, quiescent cells are not progressing in the cell life-cycle and are secreting VEGF and dead cells simply contribute to the tumour's volume but no longer have any active role. Two oxygen concentration thresholds are specified as simulation parameters: $O_{Hypoxia}$ and $O_{Critical}$, which determine the state of a cancer cell. The relation between oxygen concentration at a given position O and the state of a cell is detailed in equation 1. The transition from active to quiescent is reversible if oxygen concentrations subsequently rise again above $O_{Hypoxia}$. Logically, a dead cell may however not transition back into other states. We assume $O_{Hypoxia} > O_{Critical} > 0$.

$$state = \begin{cases} Active, & \text{if } O \geq O_{Hypoxia}, \\ Quiescent, & \text{if } O \geq O_{Critical}, \\ Dead & \text{otherwise} \end{cases} ; \quad (1)$$

1.1.4 Diffusion of Solubles

Our model incorporates the diffusion of oxygen from endothelial cells to cancer cells and of VEGF from cancer cells to endothelial cells. Concentrations of each soluble are calculated at the start of each epoch with values for each environment position updated. Given a soluble κ, equation 2 governs the diffusion process.

$$\frac{\partial \kappa}{\partial t} = D_\kappa \nabla^2 + s_\kappa - u_\kappa \quad (2)$$

D_κ is the diffusion coefficient, s_κ the source rate and u_κ the uptake (or sink) rate. The equations are solved using FiPy (Guyer et al., 1988) which implements the finite-volume method and we setup our solution using no-flux boundary conditions.

Diffusion of solubles from the intracellular space to the extracellular matrix occurs by diffusion, which means the concentration outside cells may not be greater than that inside cells. As such, source rates of individual cells may be adjusted and reduced to avoid implausible scenarios such as soluble flow against a concentration gradient. Where the inner and outer concentrations are equal the source rate effectively becomes zero.

Individual sink rates may also be adjusted to avoid negative substrate concentrations, although a minimum uptake rate must be maintained owing for examples to cells needing at least some level of oxygen. If even then a negative concentration is obtained, this indicates that the number of cells at a position exceeds the capacity of the blood vessel network and a number of cells equal to the amount required to restore positive concentrations is considered dead.

1.1.5 Angiogenesis

Angiogenesis refers to the development of new blood vessels from existing ones in response to VEGF

stimuli. Tumours secrete VEGF in conditions of hypoxia to increase the oxygen and nutrient supply. In our model, we differentiate endothelial cells in Tip and Trunk cells.

Trunk cells are static agents. They act as sources of oxygen but do not proliferate or otherwise interact with the environment. Tip cells, on the other hand, exhibit a more dynamic behavior. Given a minimum VEGF concentration, set as a model parameter, Tip cells will migrate up-gradient to an adjacent grid position. The position originally occupied will host a new Trunk cell. In-between elongations, Tip cells must complete one full cell life-cycle.

1.2 Experimental Setup

We now proceed to illustrating our experimental setup, our derivation of 2D environments from 3D ones and parametrization techniques.

1.2.1 The Target Curve

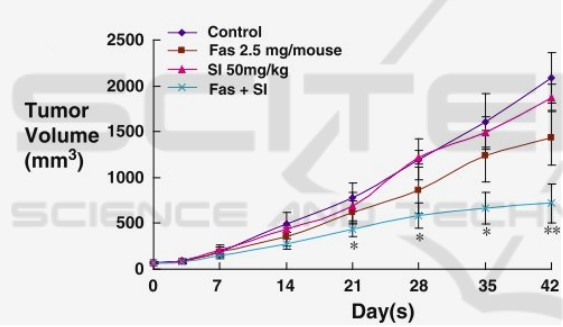

Figure 1: The target growth curves. We will be benchmarking our model against the "control" curve over the first 25 days.

We will be bench-marking against the control curve reported by *Chen et al.* (Chen et al.,) and shown in Figure 1, comparing the tumour volume obtained in our simulation to that obtained in empirical studies. We will be considering the first 2 weeks of tumour growth so as to keep the problem computationally tractable and allow us to repeat large amounts of simulations on our infrastructure. In picking the publication we would use as reference, we privileged those which reported clearly readable growth curves with a sufficient number of data-points and smaller error bars.

1.2.2 Spatial Discretization and Transformations

As mentioned earlier, the environment is discretized as a Cartesian grid. Table 1 summarizes the effective sizes of grid positions, alongside other relevant spatial values such as the volume of cancer cells and initial tumour volume. Derived 2D values are also reported.

1.2.3 Model Resolution

A decision that needs to be made upfront is the resolution of the model. That is to say, how many cancer cells will be represented by an agent. This is a compromise between model reliability and computational cost. A high number of cancer cells per agent will mean overall fewer agents necessary, but lowers the resolution (Ie: We capture a lower degree of cellular heterogeneity.), whereas a low number of cancer cells per agent provides a higher resolution but higher computational costs. Different resolutions also affect the maximum number of agents per grid position and the required initial number of agents to achieved the desired start volume or area. We will be testing three resolutions: 300, 600 and 1,200 cancer cells per agent. These are summarized in table 2.

Testing a resolution of fewer than 300 cancer cells per agent becomes computationally intractable, and decreasing the resolution to exceed 1,200 cancer cells per agent results in 2D simulations having a maximum number of agents per position of 1, which hinders either tumour growth or blood vessel development.

1.2.4 Starting Conditions

Cancer cells in an amount appropriate for a given resolution are seeded at the center of the grid. Every position in the grid is seeded with one endothelial cell. Initial soluble concentrations are calculated and assigned to positions. The simulation is thereafter allowed to run its course.

2 RESULTS

Each simulation set (Eg: 300 cancer cells per agent, 2D) comprised 200 simulations. These shared the same parameters assigned as constant values but differed in values for those assigned by grid search or random search and for those related to spatial quantities such the as maximum number of agents per position. Each simulation produced a growth curve which was compared to an expected growth curve derived

Table 1: Summary of spatial units for 2D and 3D simulations. 2D values were derived by assuming 3D structures were cuboids, and then deriving the area of the base. Values are shown to two decimal places.

3D		**2D**	
Item	**Value**	**Item**	**Value**
Volume of Cancer Cell	2,000.00 μm^3	Area of Cancer Cell	158.74 μm^2
Volume of Grid Position	0.30 mm^3	Area of Grid Position	0.45 mm^2
Start Tumour Volume	1.20 mm^3	Start Tumour Area	1.13 mm^2

Table 2: Summary of how different model resolutions affect the maximum number of agents that can be held in a grid position and the number of agents required at the start to obtain the desired initial volume or area. As expected, increasing the number of cancer cells per agent decreases both the carrying capacity of individual positions and the initial number of required agents.

Cancer Cells per Agent		**Max Agents per Grid Position**	**Initial Number of Agents**
300	2D	9	24
	3D	500	2,000
600	2D	4	12
	3D	250	1,000
1,200	2D	2	6
	3D	125	500

from medical literature. This gave an indication of the error rate for such simulation. A set's performance is calculated as the average error rate of all simulations in it. This allows, for each resolution, to compare the performance of 2D and 3D simulations. For 2D simulations, an extra step is needed to map areas back to volumes.

2.1 The Error Function

The aim of the error function is to compare the tumour growth curve produced by a simulation (in-silico curve) to the one observed in empirical laboratory studies (empirical curve). And ultimately, to produce a single value: The absolute mean error. This provides an indication of how closely an in-silico growth curve aligns to the empirical growth curve.

Expected tumour volumes at different time-points were estimated from the empirical growth curve (Figure 1).
A polynomial was then fit to these points describing the expected volume (V_{exp}) at a day (d). This is reported as equation 5, with coefficients reported to two decimal places.

$$V_{exp}(d) = 0.95d^2 + 18.10d - 65.68; 0 \leq d \leq 25 \quad (3)$$

Given the actual volume at a day d reported in a simulation's growth curve, V^d_{act}, then the error ε_d is as reported in equation 4 the magnitude of the difference between the expected and actual value.

$$\varepsilon_d = |V^d_{act} - V_{exp}(d)| \quad (4)$$

The absolute mean error of a simulation (ε) is then calculated as the average of all errors calculate at each time-point:

$$\varepsilon = avg(\varepsilon_0, \varepsilon_1, ..., \varepsilon_{d-1}, \varepsilon_d); 0 \leq d \leq 25 \quad (5)$$

2.2 Estimating Volumes from Areas

For 2D simulations, these obviously returned tumour areas. In order to compare these to expected volumes, the area was assumed to be the base of a 3D structure and the corresponding volume was derived via a simple mathematical transformation.

The generic form of this basic transformation is provided in equation 6, where V indicates volume and a area. It represents the derivation of a cube's volume from a square's area by obtaining the square's width and raising it to the cube.

$$V(a) = a^{\frac{3}{2}} \quad (6)$$

2.3 Resulting Error Rates

Error rates for 2D and 3D simulations across all resolutions are show in figure 2. For higher resolutions (Ie: Lower numbers of cancer cells represented by a single agent), 3D clearly outperforms 2D. At lower resolutions (Ie: Higher numbers of cancer cells represented by a single agent) it is the case that the two approaches appear to be comparable or that 2D outperforms 3D. This is in fact misleading and will be addressed in our discussion.

We note the stability of the error in 3D, where discrepancies of $\pm 150mm^3$ are owed to the stochastic nature of the model. As for 2D, we note that the error seems to be linearly dependent and negatively correlated to the resolution. While it might appear 2D could be as good as 3D in some instances, this is not the case and is further elaborated in our discussion.

Finally, a Welch's t-test was performed comparing the populations of errors for 2D vs. 3D at each resolution. Results were significant for across all resolutions for $p < 10^{-10}$. This t-test is appropriate as it does not assume equal population variance.

3 DISCUSSION

Our results suggest a relatively small and stable error when it comes to 3D simulations, independently of the resolution. More interesting is the 2D case, which seems to outperform 3D at lower resolutions and whose error seems to increase linearly as resolution is increased.

This might initially be interpreted as 2D outperforming 3D at all but the highest resolutions, suggesting that the former offers a viable if not preferable alternative to the latter. In fact, such is not the case. The apparent better performance of 2D is an artifact of the specific model configuration which coincidentally allows it to minimize the absolute mean error. We will discuss how 2D simulations suffer a fundamental flaw due to dimensionality mapping from 3D. We will also emphasize the importance of validation strategies which go beyond growth curve comparison, but also consider elements such as soluble concentrations and phenotype ratios within the cancer cell populations. Without these additional verifications our analysis would be incomplete and lead to the conclusion that 2D forms an alternative to 3D, whereas this is not the case.

In the first instance we note the direction of the mean error for 2D simulations. Errors are calculated as the difference between actual and expected volumes. So, a positive error means the model predicted a larger volume than expected, and a negative one that the model predicted a smaller volume than expected. A summary is reported in table 3 (see appendix). For resolutions of 300 and 600 cancer cells per agent all simulations consistently over-estimate tumour growth. For a resolution of 1,200 cancer cells per agent, a decisive majority of simulation overestimates tumour growth. It therefore appears fair to state that 2D models systematically over-estimate tumour growth.

Given that the magnitude of the error of 2D simulations increases as resolution increases, and that 2D systematically over-estimate growth, we can say that as resolution increases 2D simulations over-estimate growth by larger amounts.

To explain this we need to consider several factors. First, that as we increase resolution we decrease the number of cells per agent and therefore we increase the initial number of agents needed to keep the starting volume consistent. Given more initial agents it makes sense that the final tumour volume should be greater and that therefore the error should increase, but this does not explain why we observe this in 2D but not in 3D.

The reason behind this lies in the effect that 3D to 2D mapping and resolution adjustments combined have on the maximum number of agents per position. In 2D, a position may host between 2 and 9 agents. In 3D, between 125 and 500. (See tables 1 and 2.) This means that in 3D we may obtain a much higher cancer to endothelial ratio at each position than in 2D. This is because cancer cells produce daughter cells each capable of dividing, resulting in exponential growth, whereas a tip cell will only produce another tip cell and trunk cell, the latter being unable to divide, leading to linear growth.

In both 3D and 2D cancer cells will exceed endothelial cells but, crucially, in 2D space constraints means the ratio will never increase to the point where oxygen becomes a limiting factor. This is owed to the source rate of oxygen being much higher than its sink rate, and an endothelial cell being able to support multiple cancer cells. Unless enough space is allowed at a position for a significant amount of cancer cell divisions, these will never exceed the capacity of the initial blood vessel network.

In summary, in 2D simulations oxygen never becomes a limiting factor of growth meaning that a higher number of initial cancer cells, as is seeded at higher resolutions, results in a larger final tumour volume. In 3D instead oxygen may become a limiting factor and modulates and restricts tumour growth.

Our results raise important considerations for tumour modelling. Where simulations implement a 2D environment, appropriate scales and parameter values need to be chosen to avoid issues similar to those we described which would make the models biologically implausible. Specifically, parameter values derived from 3D studies (such as empirical ones in laboratories) should not simply be copied over to 2D in-silico experiments without consideration being given to the change of dimensionality. However, publications rarely discuss the process of deriving their 2D environments from 3D ones.

Consideration should be given to the use of re-

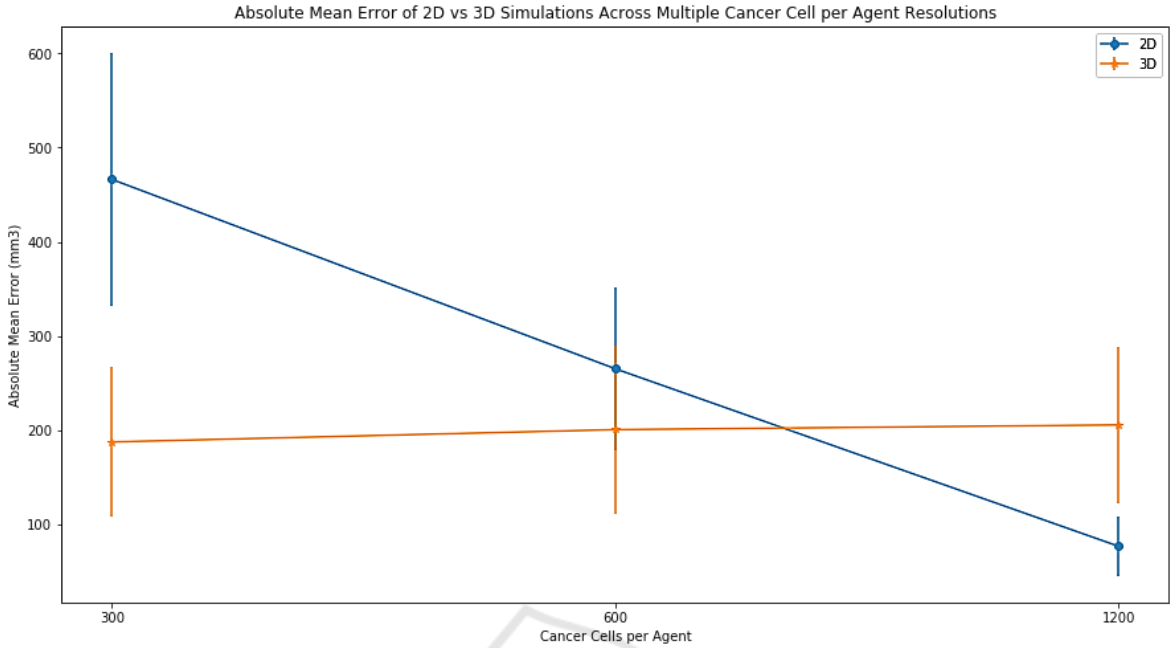

Figure 2: Summary of error rates for each resolution, 2D vs. 3D. Error bars represent standard deviation on the mean. A higher number of cancer cells per agent indicates a lower resolution, as this means the simulation is modelling larger groups of cells together rather than allowing them to develop independently.

Table 3: For each resolution we report the number of 2D simulations which over-estimate tumour growth (positive error) against the number that under-estimate tumour growth (negative error).

Resolution (Cancer Cells per Agent)	**Number of Positive Errors**	**Number of Negative Errors**
300	196	0
600	194	0
1,200	187	12

medial action to make 2D models viable. For example, by implementing strategies to increase sink rates or decrease source rates of oxygen. Or, alternatively and among other possible approaches, decoupling the maximum number of cells per position from the overlying 3D model from which a 2D one has supposedly been derived. While these approaches may produce apparently valid results, the question then is what impact does the aforementioned set of remedial actions have on the reliability of results. For example, setting the maximum number of agents per cell to an arbitrary value may result in a model accepting unrealistic cell concentrations in tissues. Or, tweaking source and sink values may result in the model working with hyper- or under-oxygenated tissues.

More importantly, enforcing artificial constraints on the model subtracts from its emergent behaviors. The main value of these models lies in them revealing unexpected and insightful patterns from a set of simple, underlying rules. Developers should specify the behavior of individual agents so that they mimic as closely as possible their biological counterparts. Developers should not try to direct the evolution of the model in a specific direction as they would be doing when imposing remedial strategies. To do so would be to constrain the simulation setting it up towards a specific conclusion or end-state, which would limit its usefulness towards gaining additional understanding of biological phenomena.

It is worth adding some biological considerations to the limitations of 2D models we discussed. Alongside unrestricted growth where oxygen is no longer a limiting factor, other properties of tumours will result as altered. In 2D we will not observe regions of hypoxia in the cancer mass, nor the formation of a necrotic core. Secretion of VEGF will not occur, which in turn will lead to no angiogenesis or blood vessel developent. In simulations where these were implemented, hypoxia-inducible factor (HIF) pathways would not be activated. HIF pathways mediate significant phenotypic alterations in cancer cells (Philip et al., 2013; Semenza, 2007), which would

therefore not be observed in 2D. It is therefore clear how the impact of oxygen concentrations on 2D models significant affects the accuracy and reliability in a negative manner.

We also emphasize the numerical scale of our simulations. Confidence in our results is further reinforced by running 200 simulations per simulation set. (A simulation set refers to, for example, the group of 2D simulations having 300 cancer cells per agent) This reduces the likelihood of results being due the stochastic nature of the model, allowing us to infer that they are truly representative of the model's behavior.

This contrasts with other publications surveyed, where the number of simulations run is not discussed. Given models often include elements of stochasticity, it is important for multiple iterations of these to be evaluated so as to obtain a clearer picture of their underlying behavior and evolution. Multiple runs also allow to explore the search space for parameters whose value has not been established with certainty, assessing the model's sensitivity to changes in these and informing us about the impact on the results of the simulation. Search strategies for parametrization, such as but not limited to grid and random search, should be explicitly mentioned and discussed. Distribution parameters should be reported, as well as the number of draws from each distribution and relevant information. This is necessary for experimental reproducibility.

We will now consider costs. We ran our simulations on Amazon AWS EC2 instances of class r4.large. These feature 2 vCPUs and 16GiB of RAM. The cost of these is between $0.01 and $0.001 per hour depending on the specific plan selected. A single 2D simulation took on average one hour and a single 3D simulation on average four hours. We will also note that while we used a large fleet of instances to run a high number of simulations, individual simulations could be run in reasonable time within an average office laptop.

Hence, the price of simulations in 2D or 3D is comparable. Even for the more expensive 3D simulations, a single simulation set comprising 200 simulations will still cost under $1. Given the severe limitations of 2D we discussed, and the negligible differences in computational and dollar cost, we think our investigation makes a very strong case for 3D as the sole viable solution.

In summary, careless or approximate mapping of 3D environments into 2D ones, or creation of 2D environments without consideration for their 3D counterparts, raises questions about the validity of the model. Where this discussion is omitted, as is the case in many publications, this impacts the reliability of results as it is not clear what accuracy or resolution has been achieved by the model. Further, due to the negligible difference in costs between 2D and 3D, we believe there is a clear case for the latter to be preferred over the former.

4 CONCLUSION

We have developed an agent-based model of tumour growth with continuous elements to account for soluble diffusion and simulated tumour growth in 3D and derived 2D environments at multiple resolutions of cancer cells per agent. We have addressed the issue of parametrization by wherever possible relying on values in literature, and where these were unknown using well-established search techniques such as grid search and random search.

Error rates for each simulation were calculated by comparing growth curves produced by our model to those reported in literature, and at each resolution we compared error distributions and average error values for 2D and 3D. Initial results suggested, purely on based on error rates, that 3D simulations consistently produced low error rates and outperformed 2D at higher resolutions. On the other hand, 2D simulations outperformed 3D at lower resolutions and their error was dependent on the resolution.

Further analysis revealed that the combined impact of cancer cells per agent resolution and 3D to 2D mapping significantly altered the topology of the 2D environment. Because of this oxygen concentrations, a factor limiting growth in 3D, no longer affected tumour growth in 2D. As a result, tumour growth in 2D became predominantly a function of the initial volume and was no longer modulated by oxygen availability as is the case in 3D.

These results highlight the challenges of simulating a phenomenon that occurs in 3D, such as tumour growth, in 2D. Neglecting to explicitly derive the 2D environment from a 3D one, as many publications do, raises questions about the validity of the model and realibility of the results.

In conclusion, our results suggest that 3D models should be preferred to 2D ones. In cases where 3D ones may not be implemented, a clear discussion should be provided regarding the derivation of the 2D model from a 3D one.

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