

# A numerical approach to modelling avascular tumour evolution with white noise

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## Abstract

In this paper, a model for avascular tumour growth with white noise is presented. The model is essentially formulated as a set of partial differential equations describing the spatio-temporal evolutions of cell concentrations based on reaction-diffusion dynamics and the law of mass conservation. Perturbations in the form of white noise are introduced to model the effects of random processes on distinct time scales. A numerical approach is used to solve the system and numerical simulations in one and two space dimensions are presented. Numerical results indicate that the proposed model is a reasonable approach that may be used to examine the effects of nutrient supply in tumour growth dynamics.

## Contents

|          |   |          |
|----------|---|----------|
| <b>1</b> | <b>Introduction</b>                         | <b>2</b> |
| <b>2</b> | <b>Tumour growth model with white noise</b> | <b>3</b> |
| <b>3</b> | <b>Numerical solution</b>                   | <b>5</b> |
| <b>4</b> | <b>Results and discussion</b>               | <b>6</b> |
| <b>5</b> | <b>Conclusion</b>                           | <b>9</b> |

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# 1 Introduction

This paper focusses on the growth dynamics of the avascular tumour. After the early stages of growth, a multicell spheroid typically consists of an inner zone of necrotic cells and an outer zone of living cells. The outer zone can be further divided into a layer of quiescent cells and a layer of proliferating cells. Quiescent cells are alive, but do not proliferate due to nutrient deprivation.

Figure 1 illustrates the development of a mass of tumour cells to the typical three layer structure of a multicell spheroid consisting of a thin outer shell of proliferating cells, an inner region where cells are dormant but viable, and a central region of necrotic material.

Modelling of avascular tumours are often seen as a first step towards developing more models for later stages of tumour growth. In recent years, many different types of mathematical models have been developed to describe avascular tumour growth. The first theoretical study that proposes that diffusion and nutrient consumption might be limiting solid tumour growth was probably carried out by Burton [6]. Since then, numerous studies have been developed to describe the spatio-temporal interactions between tumour cell populations and nutrients.

Early models of nutrient-limited tumour growth have assumed nutrient concentration profiles to be a function of tumour spheroid radius which changes due to cell proliferation. An example is the influential study by Greenspan, where tumour cell populations are divided into proliferating, quiescent and necrotic sub-populations [10]. Greenspan's model attempts to determine the location of the interfaces between the compartments which are controlled by the nutrient levels. This approach, based on the tumour spatial structure, has since been used widely by other researchers (see, for example, [2], [3], [15] and [17]).

Of late, there have been attempts at building stochastic models for tumour growth. Albano and Giorno proposed a stochastic model based on deterministic Gompertz law in a one-dimensional diffusion process [4]. Similarly, Lo proposed a stochastic Gompertz model for tumour cell growth in which a therapy term may be added to examine its effects [12].

In this paper, white noise is introduced to a reaction-diffusion model for avascular tumour growth. A numerical approach is then employed to solve the set of governing model equations. A simulation of tumour growth in two dimensions is also presented to provide a better visualization of the growth process.

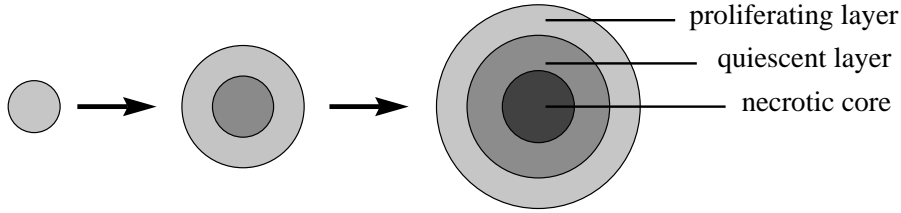


Figure 1: Schematic illustration showing the growth of a tumour and the formation of the proliferating and quiescent layers, and the necrotic core

## 2 Tumour growth model with white noise

The tumour growth model considered here is based on a compartment-model shown in Figure 2. Originally proposed by Sheratt and Chaplain [14], this model treats the in vivo tumour as a continuum of proliferating, quiescent and necrotic cells, whose densities are denoted by  $p(x, t)$ ,  $q(x, t)$  and  $n(x, t)$  respectively, where  $t$  and  $x$  are time and the one-dimensional space coordinate respectively.

In the model, the mitosis rate  $g(c)$  of the proliferating cells is assumed to be proportional to the concentration of nutrients and limited by the crowding effects of the total cell population. It is assumed that nutrients pass through the surface of the tumour and diffuse into the interior through the intracellular space fast enough for the local nutrient concentration,  $c(x, t)$  to be quasi steady. In the direction of the core of the tumour, some proliferating cells with limited access to the intracellular nutrients become quiescent at rate  $f(c)$ , and some quiescent cells which are totally deprived of nutrients undergo necrosis at rate  $h(c)$ .

The presence of one cell type limits the movement and growth of another cell type. This is known as contact inhibition of migration [1]. In order to include the effects of contact inhibition in the the present model, the overall viable cell flux is fractionated evenly between the proliferating and quiescent cell densities. It is assumed that the two cell populations have equal motility. The movement terms of the proliferating and quiescent cells are thus  $\frac{\partial}{\partial x} \left( \frac{p}{p+q} \frac{\partial(p+q)}{\partial x} \right)$  and  $\frac{\partial}{\partial x} \left( \frac{q}{p+q} \frac{\partial(p+q)}{\partial x} \right)$  respectively.

Applying the law of mass conservation to the cells, the set of governing equations for the evolution of  $p(x, t)$ ,  $q(x, t)$  and  $n(x, t)$ , and the equation for

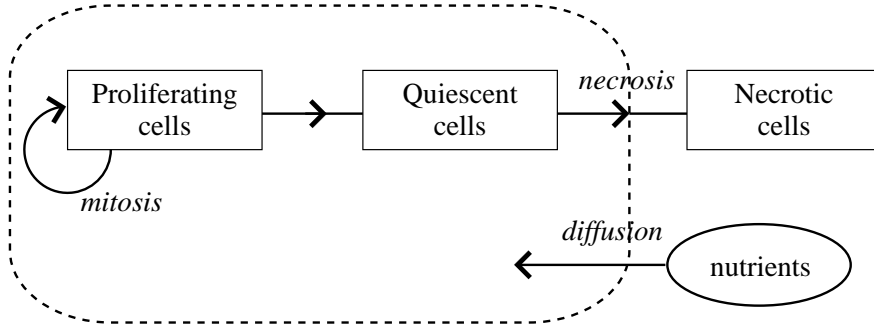


Figure 2: A compartment-model for tumour growth: proliferating cells may multiply through mitosis, or become quiescent cells, which in turn may undergo necrosis

$c(x, t)$  may be written as follows.

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} \left( \frac{p}{p+q} \frac{\partial(p+q)}{\partial x} \right) + g(c)p(1-p-q-n) - f(c)p \quad (1)$$

$$\frac{\partial q}{\partial t} = \frac{\partial}{\partial x} \left( \frac{q}{p+q} \frac{\partial(p+q)}{\partial x} \right) - f(c)p - h(c)q \quad (2)$$

$$\frac{\partial n}{\partial t} = h(c)q \quad (3)$$

$$c = \frac{c_0}{\gamma + p} (1 - \alpha(p + q + n)) \quad (4)$$

Equation 4 represents the access of nutrient from underlying tissue. By assuming that the effectiveness of this source term decreases with overall cell density, the parameter  $\alpha \in (0, 1]$  represents a constant of proportionality and  $c_0$  is the nutrient concentration in the absence of a tumour cell population. It is assumed that the cells are completely closed-packed at the maximum non-dimensionalised cell density of 1. In subsequent numerical computations, the total tumour cell density given by  $p + q + n$  is set to 1 for convenience. The functions  $f(c)$  and  $h(c)$  are assumed to be decreasing with  $h$ . A Gompertz growth rate is used to represent the mitosis term in the formulation of  $g(c)$ .

Given the random effects due to the disparate cell clones, cell stress and inhibiting factors considered in this model, it is appropriate to inject a stochastic component to the model. One approach is to introduce white noise to the Equation 3, the necrosis equation. The result is the following equation in differential form,

$$\partial n = h(c)q\partial t + q\tau dW(t) \quad (5)$$

where  $W(t)$  is the standard Wiener process and  $\tau$  is a scaling parameter.

Equations 1, 2, 4 and 5, together with functions  $f(c)$ ,  $g(c)$  and  $h(c)$ , form a set of equations that model the evolution of cells with white noise perturbations in an avascular tumour.

### 3 Numerical solution

The system of equations 1, 2, 4 and 5 may be discretized using a forward difference approximation for time derivatives and central difference approximations for space derivatives. The resulting set is

$$p_i^{j+1} = p_i^j + \Delta t (u_i^j + g(c_i^j)p_i^j (1 - p_i^j - q_i^j - n_i^j) - (f(c_i^j)) p_i^j) \quad (6)$$

$$q_i^{j+1} = q_i^j + \Delta t (v_i^j + f(c_i^j)p_i^j - h(c_i^j)q_i^j) \quad (7)$$

$$n_i^{j+1} = n_i^j + \Delta t (h(c_i^j)q_i^j) + \tau q_i^j (W_i^{j+1} - W_i^j) \quad (8)$$

$$c_i^j = \frac{\gamma}{\gamma + p_i^j} (1 - \alpha (p_i^j + q_i^j + n_i^j)) \quad (9)$$

where

$$u_i^j = \frac{(p_{i+1}^j - p_{i-1}^j)r_i^j(r_{i+1}^j - r_{i-1}^j) + 4p_i^j r_i^j (r_{i+1}^j - 2r_i^j + r_{i-1}^j) - p_i^j (r_{i+1}^j - r_{i-1}^j)^2}{4(\Delta x)^2 (r_i^j)^2}$$

$$v_i^j = \frac{(q_{i+1}^j - q_{i-1}^j)r_i^j(r_{i+1}^j - r_{i-1}^j) + 4q_i^j r_i^j (r_{i+1}^j - 2r_i^j + r_{i-1}^j) - q_i^j (r_{i+1}^j - r_{i-1}^j)^2}{4(\Delta x)^2 (r_i^j)^2}$$

$$r_i^j = p_i^j + q_i^j$$

and  $\Delta t$  and  $\Delta x$  refer to the time steps and space intervals respectively for the finite difference scheme. In the above equations, the superscript and subscript represent the time level and space position respectively.

The Euler-Maruyama (EM) method for solving stochastic differential method numerically as suggested by Higham is used here [11]. A discretized Brownian path over  $[0, T]$  with a prescribed incremental value of  $\delta t$  is first computed. Equation 8 is then solved by applying the EM method, with a stepsize of  $\Delta T = R\delta t$ , for some  $R \in \mathbf{Z}^+$ . This ensures that the set of points on which the discretized Brownian path is based contains the points of the EM computation. On a general step, the EM method requires the increment  $W_i^{j+1} - W_i^j$ , which is given by

$$W_i^{j+1} - W_i^j = W((j+1)R\delta t) - W(jR\delta t) = \sum_{k=jR+1}^{(j+1)R} dW_k \quad (10)$$

Table 1: Functional forms and parameter values used in present model

| Functions                               | Possible Parameter values      |
|---|--------------------------------|
| $f(c) = \frac{1}{2}(1 - \tanh(4c - 2))$ | $\gamma = 10, \quad c_0 = 1$   |
| $g(c) = \beta e^{\beta c}$              | $\beta = 0.1 \text{ to } 1.0$  |
| $h(c) = \frac{1}{2}f(c)$                | $\alpha = 0.2 \text{ to } 0.9$ |

with  $W(0) = 0$ .

For boundary conditions, we set  $\partial p/\partial x = 0$  and  $\partial q/\partial x = 0$  at  $x = 0$  and as  $x \rightarrow \infty$ . At  $t = 0$ , we assume there are no quiescent and necrotic cells. Thus, we set  $q(x, 0) = n(x, 0) = 0$ . At the beginning of any tumour growth, there would be a high concentration of proliferating cells near the point of genesis. The density of proliferating cells decreases with distance from the point of genesis. Thus, it is assumed that  $p(x, 0)$  takes the form of a decreasing exponential function.

Functional forms of the rates  $f(c)$ ,  $g(c)$  and  $h(c)$  will affect the results. For this discussion,  $f(c)$  and  $h(c)$  have been intentionally chosen to coincide with those used in [14] and [16] for comparison purpose, while  $g(c)$  is given a Gompertz growth formulation as discussed earlier. Similarly, values for various parameters in the model are chosen to be those used in either [14] or [16]. A summary of the parameters and functions is given in Table 1.

In the present study, we let  $p(x, 0) = 0.01 \exp(-0.1x)$ , and set  $\delta t = 0.05$  and  $R = 2$ . In solving the finite difference equations, we let  $\Delta t = 0.004$  and  $\Delta x = 1$ . For the current discussion, we set the duration of the simulation to be  $T = 14$  (in arbitrary time units). As for the one-dimensional space, theoretically, the domain is  $[0, \infty]$ . In practice, however, the numerical computations may terminate when  $x$  is sufficiently large. Numerical experiments indicate that  $x = 210$  may be deemed far enough if  $\Delta x = 1$ .

The Box-Muller pseudo-random number generator is used to generate a set of random numbers for from a Normal distribution with mean 0 and variance 1 (see [5]). The code was written in Visual Basic for Applications (VBA) and compiled and run on a Pentium 4 system. Computation was stable for the chosen set of parameters and convergence was rapid.

## 4 Results and discussion

The model is solved for the set of parameters, functions, boundary and initial values mentioned above. Values of  $\alpha$  ranging from 0.2 to 0.9 were used in the simulation runs to investigate the effects of variable nutrient supply on tumour growth dynamics. Results for representative cases  $\alpha = 0.4$  and

$\alpha = 0.8$ , with  $\beta = 0.5$  are presented and discussed here.

Figures 3 and 4 show the simulation results of the model. The simulation shows an asymmetric spatial distribution of an advancing pulse of proliferating cells  $p$ , with a band of quiescent cells  $q$  and a necrotic core  $n$  in a radial direction at times  $t = 0, 2, \dots, 14$ .

From  $t = 2$  to  $t = 8$ , the initial necrotic cell density is distributed inwards of the tumour core. As time passes, the necrotic cells continue to internalize with some necrotic cells dispersing towards the outer edge of the tumour due to the distribution of the nutrient access as well as the stochastic perturbation present in the model. That is, further towards the tumour outer edge, some of the proliferating and quiescent cells are converted to necrotic cells due to lower nutrient concentration.

While the necrotic cell density is building up with time, no tumour regression is detected. As time evolves, the proliferating and quiescent cells are still propagating with no observed decrease in densities. These results compare well with that obtained by Nirmala et al [13]. Both model and experimental results report no limiting spheroid volume. Instead, Nirmala et al observed growth of the total volume of the spheroid over time.

The results of the simulation presented in Figure 4 demonstrated growth differences between the tumour subpopulations of proliferating, quiescent and necrotic cells. Other than the diffusion limited nutrient supply and the heterogeneity in each of their own growth dynamics, the regulation of the tumour growth characteristics could possibly be attributed to the stochastically perturbed tumour environment. The stochastic perturbation is assumed to occur in response to random processes brought about by the disparate cell clones, cell stress and the inhibiting factors considered in this model.

By varying the nutrient coefficient,  $\alpha$ , tumour cell distributions change over time. At a lower  $\alpha$  value of 0.4, and hence, driven forward by the increased access of nutrient from the surrounding tissues of another body site, Figure 3 shows the live tumour cell distribution is built to a higher level over a shorter length of time and longer span of space. The layer of live tumour cells thickens and the necrotic core diminishes in size. While there is a significant increase in the proportion of proliferating tumour cells in the presence of a simulated rich supply of nutrients, the tumour expansion rate is observed to be unaffected. These results are consistent with the argument that tumour growth is influenced not only by the availability of nutrients, but also by the stochastically perturbed tumour environment.

The simulation results also show that when  $\alpha$  is decreased, part of the proliferating cell density at  $t = 14$  is being distributed in the necrotic core. As compared to the random effects considered in the cell proliferation rate and the nutrient level in the model proposed in Tan and Ang [16], the stochastic

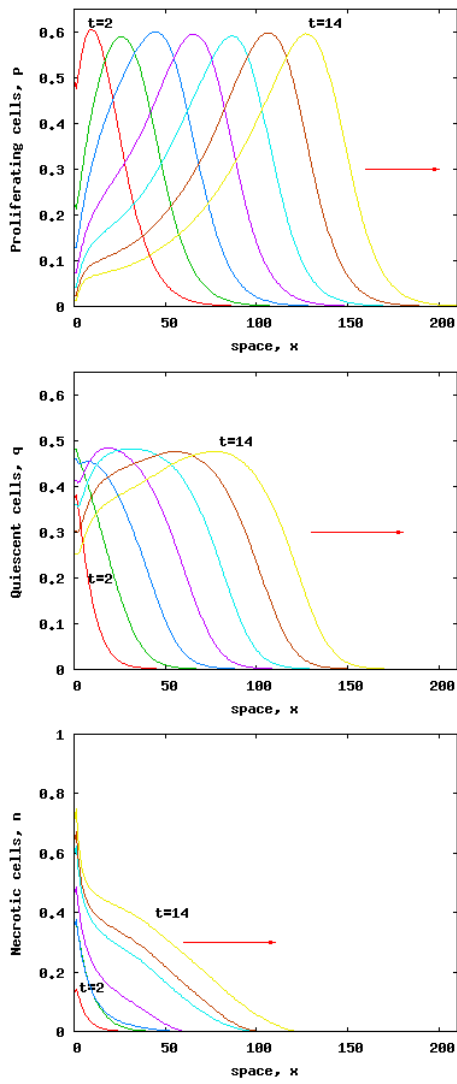


Figure 3: Evolution of proliferating, quiescent and necrotic cells at  $t = 0, 2, \dots, 14$ , for  $\alpha = 0.4$

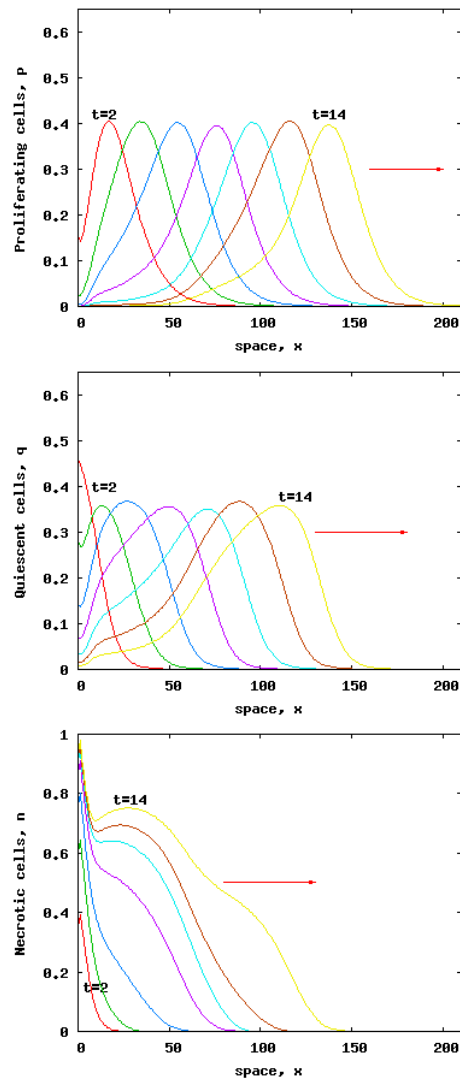


Figure 4: Evolution of proliferating, quiescent and necrotic cells at  $t = 0, 2, \dots, 14$ , for  $\alpha = 0.8$

perturbation in the present model assumes the form of a white noise process incorporated in the necrotic cell growth dynamics. The observed response of the actively proliferating cells against the necrotic core pressure suggests that tumour growth dynamics could likely be impacted by the stochastic perturbation.

Assuming radial symmetry, a simulation of tumour growth in two dimensions may be constructed. In Figure 5, a series of snapshots of tumour growth generated in this manner is presented. At  $t = 2$ , tumour growth is initiating naturally with a higher concentration of proliferating than quiescent and necrotic cells. At  $t = 6$ , we begin to observe that there are not only cells moving towards the periphery but that a significant number of quiescent and proliferating tumour cells are moving from the periphery towards the core area. This simulated internalization of tumour cells agrees well with the experimental work by Dorie et al [7].

From  $t = 4$  to  $t = 8$ , the tumour is observed to be growing very fast in the initial nutrient rich condition. As the tumour grows in size, the availability of nutrients decreases towards the centre, with growth retardation observed from  $t = 10$  to  $t = 12$ . This observed growth rate is consistent with experimental works on diffusion-limited tumour growth [9].

At  $t = 14$ , the three layer structure of multicellular spheroid experimentally observed by Folkman and Hochberg in [8] and represented in Figure 1 is formed with a distinct necrotic core. It can be seen from the figure that the present model has produced fairly acceptable results which are in good agreement with experimental works.

## 5 Conclusion

This paper discusses a tumour growth model that includes white noise. Numerical results and qualitative comparisons with published works indicate that the model presented is a reasonable model. It should be noted however that the tumour dynamics responsible for the stochastic perturbation has not been determined experimentally. The results shown in this study only speculate the true nature of the tumour cell distribution based on the assumptions of the model. Further experimental input is required to determine the actual phenomena contributing to stochastic processes in tumour growth. We also note that the stochastic perturbation in the current model is applied with respect to time. One may expect not only the temporal but also the spatial scale of the white noise processes to have significant influence on tumour growth. Future studies will therefore need to address this issue.

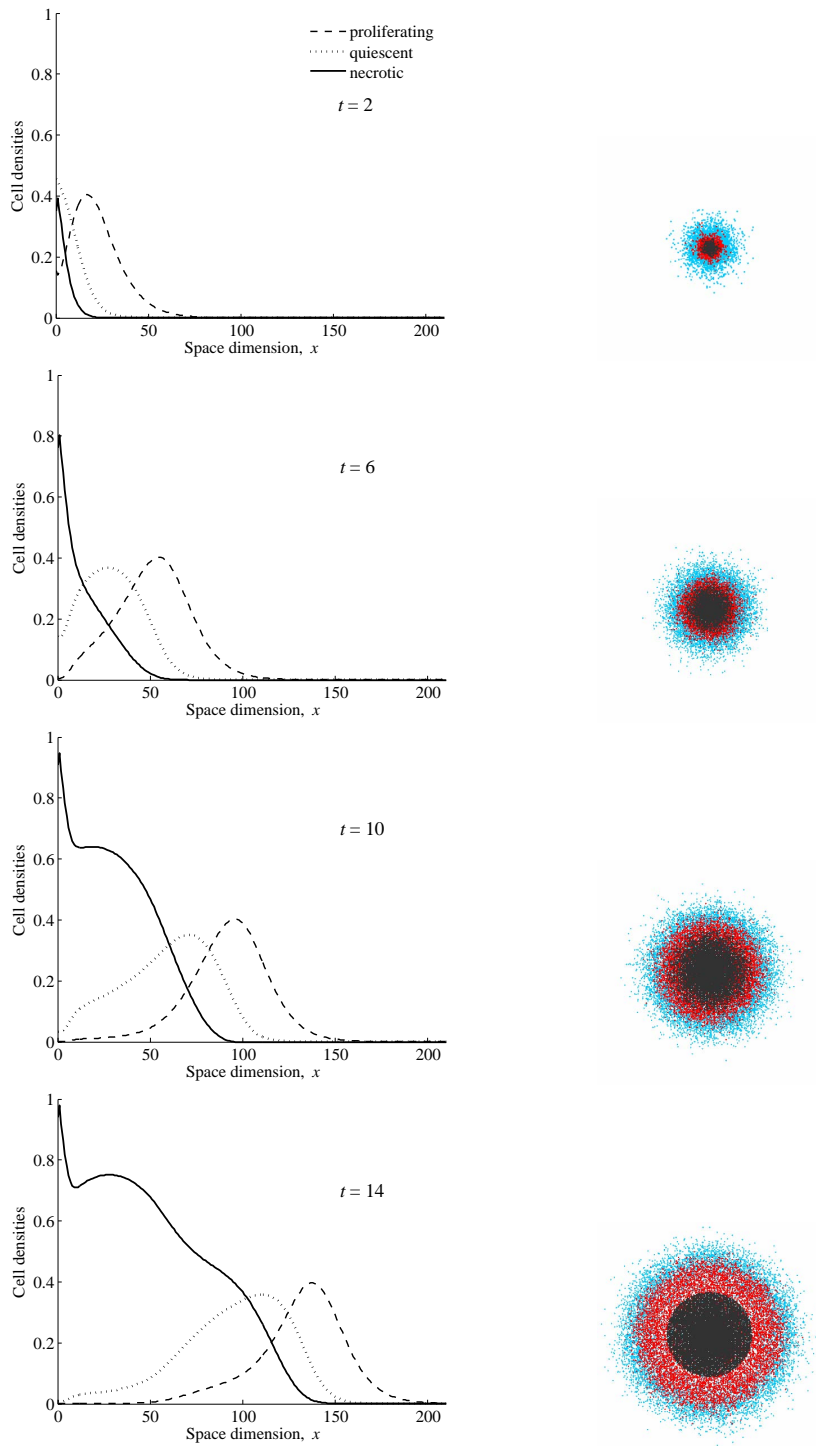


Figure 5: Spatial-temporal evolution of avascular tumour cells with white noise. Graphs and snapshots of growing tumour spheroid at  $t = 2, 6, 10,$  and  $14$  show formation of proliferating, quiescent and necrotic cells.

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