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DELFT UNIVERSITY OF TECHNOLOGY

REPORT 16-05

LITERATURE STUDY ON CELL-BASED SEMI-STOCHASTIC MODELLING
FOR THE DYNAMICS OF GROWTH OF CELL COLONIES

J. CHEN, F.J. VERMOLEN

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Delft University of Technology

Literature study on cell-based semi-stochastic modelling for the dynamics of growth of cell colonies

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Contents

1	Introduction	2
2	The mathematical model	5
3	Numerical method	8
4	The numerical simulations	9
4.1	Parameter Values	9
4.2	Results.....	10
4.2.1	Cell migration and division.....	10
4.2.2	Tumor growth.....	15
5	Conclusion and outlook	17
5.1	Improving the probability for cell division and death	18
5.2	Incorporating more factors.....	18
5.3	Wound healing simulation.....	19
5.4	Angiogenesis simulation.....	19
5.5	A parameter variation study	19
5.6	A three-dimensional simulation	20

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Abstract

Cancer, known as an uncontrolled malignant tumor, forms from cancer cells, which assemble to colonies with large numbers. This report deals with a cell-based model that describes the very stages of cancer in two spatial dimensions. Cell migration, proliferation, mutation as well as apoptosis (programmed cell death) are dealt with in the present formalism, where the mechanical strain energy density determines the rates of these cellular processes. Cellular displacement is modelled through the solution of a large system of ordinary stochastic differential equations where the deterministic and stochastic parts, respectively, follow from the strain energy density and from random walk. The stochastic differential equations are solved by the use of the classical Euler-Maruyama method. The report deals with a parametric study, and treats some implications from the model like exponential growth of cancer in the early stages at the expense of the constituent cells in the tissue.

1 Introduction

Cancer, known as a malignant tumor, is in the top two of causes of threat to human life. Malignant neoplasm cells proliferate in an uncontrolled fashion, which have a potential to diffuse to other parts of body and thereby invading healthy tissue and organs. More than 100 different types of cancers (such as lung cancer, breast cancer, colon cancer, pancreatic cancer, *etc.*) lead to human death. Unfortunately, the number of casualties increase dramatically every year [1, 2].

There are several factors that could arouse tumors to occur. We mention the following most significant ones: 1) nitrosamines, alkylating agents and other chemical factors; 2) ionizing radiation, x ray and related physical factors; 3) virus and biological factors; 4) human internal factors including hereditary, immunity and endocrine problems. Those combined factors infer that the DNA of normal cells is damaged non-lethally, proto-oncogenes are activated and/or suppressor genes can be inactivated. Furthermore, apoptosis regulating

genes and/or DNA repairing genes possibly change, which eventually lead to cell transformation. Then local transformed cells possibly lose their regulation of growth, which result in abnormal proliferation and differentiation at the gene level.

The rate of tumor growth depends on the speed of cancer cell division and death, further, cell division depends on the number of mitotic cells. By animal experiments, scientists found that the number of cancer cells grows exponentially at the beginning and that the growth rate subsequently gradually slows down as the number of cancer cells becomes large. The reason for this phenomenon is inadequate nutrition, which inhibits the cancer cell mitosis and leads to death. This is also observed in cell colonies that are subject to a limited food supply. In these colonies, the population behaves according to the well-known logistic equation and thereby the number of cells typically exhibits a so-called S-curve. For in vitro experiments, it has been observed that if the distance between dividing cells and the nutrients exceeds three cell layers, then cancer cells enter the dormant stage G0 and subsequently the phase of necrosis [3]. This phenomenon is well-observed in fast-growing tumors. However unfortunately, for diagnosed cancer patients, the numbers of cancer cells normally level off after the initial exponential growth phase and further they start to migrate by diffusion and other taxis-mechanisms, and therefore, the tumor loses its stage of being isolated and thereby the best period for treatment has elapsed. Therefore research related to growth characteristics of cancer cells and to their proliferation is really essential for early cancer detection and as well as for the time of diagnosis, which could lay the foundation for improvement of cancer therapy.

For tumor research, biological experiments form a traditional and important approach, and hence the community has accumulated a wealth of experience and obtained a lot of knowledge about the dynamics of tumor initiation and growth. However, for cell growth and its regulated mechanisms, the availability of experimental data and results is still limited. Therefore, there is an urgent need to strengthen multidisciplinary tumor research including branches from medicine, biology, statistical physics, engineering and mathematics. In the past the dynamic behaviour and the stability conditions in the time domain have been simulated using zero-dimensional models [4]. Progress in modelling, biological insights and the increase of computational resources have facilitated simulations of tumor growth and development over time as well over space. Some studies seem to indicate that all processes in the universe follow a similar rule and that they can be concisely expressed in mathematical equations, which enables understanding the evolution of these processes by studying mathematical equations and models. Currently, there are different mathematical models for tumor growth, most of which are based on solving partial differential equations for cell densities [5]. Olivier Clatz *et al.* [6] used a model to simulate the growth of glioblastomas multiform (GBM), which enables the improvement of therapy planning by defining the invasion margins by the use of the estimation of the cancer cell density. Vermolen *et al.* [5] simulated tumor initiation combined with the immune response using stochastic processes, secretion of chemokines, as well as models for random walk, haptotaxis and cell-cell contact forces, which offers a more accurate and valuable simulation framework for cancer drug treatment. Folkman [7] proposed that solid tumor growth is divided

into an avascular phase and a vascular phase. During the avascular phase, tumor grows slowly, because cancer cells exchange chemicals relying on diffusion. However, a tumor will start the complex process of angiogenesis once growth is restricted by inadequate nutrition or oxygen tensions, which is a key transition from the benign dormant mode (avascular phase) to the malignant soaring mode (vascular phase). During the last mentioned phase, oxygen and necessary nutrition are transported by new blood vessels to the tumor, such that it is able to expand in volume and to penetrate and seed into other vital parts of the body. Bookholt simulated the development of the vascular network around the tumor (angiogenesis) by the use of a so-called cell-based formalism, as well as by the use of the cellular Potts model [8].

Currently, a variety of numerical methods have been reported for solving problems. Vermolen [5] used explicit time-integration methods relying on the Euler Forward method, which not only solves the discontinuous contact mechanics, but also limits the cell migration distance during a time-interval. He also used finite-element method to evaluate the concentrations which decides the migration of cells or its boundary problems as well as mechanical displacement. Another alternative numerical strategy is cellular Potts, and Merks and his colleagues [9] used this method to modelling angiogenesis, after which this approach was improved by Lemmon [10] and Van Oers [11].

Developing new insights into tumor behavior and response in connection with its environment needs an intimate link between experimental results and the development of hypotheses. In order to facilitate this link and in order to be able to forecast this tumor behavior under circumstances that lie beyond the available experimental results, a quantification of the hypotheses into mathematical relations is indispensable. Therewith, mathematical models are needed. Since the main research objective is to gain understanding on the initiation of the tumor, we will make use of cell-based modelling frameworks. The models to be used aim at gaining quantitative insight into the underlying biological mechanisms and using these quantitative relations. Therewith we think that tumor treatment in terms of therapy and prevention can benefit from the mathematical simulation methods that we will develop. Furthermore since the models are cell-based with individual cells proliferating, differentiating, mutating, migrating and dying, the simulation outcomes can be visualized easily and hence be used for illustrational purposes for patients, doctors, students and pharmaceutical companies.

For this report, we firstly introduce the mathematical model for initial stages of cancer cells. Subsequently, the numerical methods will be presented, which is followed by some simulations with two cells and with larger cell colonies. Finally, we discuss the model and give some future plans.

2 The mathematical model

In this section the mathematical framework for simulating the early stages in the development of cancer is presented in terms of the equations. We consider a flat two-dimensional substrate labelled by $\Omega \in \mathbb{R}^2$, on which cells are allowed to undergo all biological processes and where the chemicals are allowed to be secreted and to diffuse. To encode a mathematical model, the following assumptions are used in the development of the present formalism: 1) all cells are hemi-spherical and the projection onto the two-dimensional substrate is a circle; 2) each cell has two discrete states: viable or dead; 3) at time t , $n(t)$ cells are on the domain; 4) each viable cell exerts a traction force and moves; 5) all viable cells have same the maximal traction force F_i and the traction force of a dead cell is zero; 6) all viable cells detect the deformation of the substrate provided the signal exceeds a critical value; 7) the cells that detect the substrate deformations induced by the other cells will tend to migrate to one-another; 8) cells that collide into one-another repel each other by the contact forces that they exert in the normal direction.

Traction force is crucial for cell migration and as well as for, among others, shape maintenance and mechanical signal generation [12]. Cells generate internal tensile force through actomyosin interaction and exertion on the attached substrate or extracellular matrix. Slight deformation of the substrate caused by a stress gives a strain energy, which reads as:

$$U = \frac{1}{2}V\sigma\epsilon = \frac{1}{2}VE\epsilon^2 = \frac{1}{2}\frac{V}{E}\sigma^2, \quad (1)$$

where V denotes the deformation volume, σ denotes stress, ϵ denotes strain of the substrate at the centre of cell and E is the Youngs modulus from Hooke's law, given by

$$E = \frac{\sigma}{\epsilon}, \quad (2)$$

We use M_i^0 to represent the strain energy density, that is the energy per unit of volume, which follows from the exertion force F_i at the position of cell i . Then the strain energy density is dictated by

$$M_i^0 = \frac{1}{2}\sigma\epsilon = \frac{1}{2}E_s(\mathbf{r}_i)\epsilon^2 = \frac{1}{2}\frac{\sigma^2}{E_s(\mathbf{r}_i)}, \quad (3)$$

where $E_s(\mathbf{r}_i)$ represents the local elasticity modulus of the corresponding substrate. The above relation is able to handle the non-uniformity of the substrate stiffness. Further, \mathbf{r}_i denotes the position of cell i . If we use L and d for the thickness and vertical displacement of the deformed substrate, then ϵ is given by

$$\epsilon = \frac{d}{L}, \quad (4)$$

and hence the strain energy density can be calculated by

$$M_i^0 = \frac{1}{2}E_s(\mathbf{r}_i)\left(\frac{d}{L}\right)^2. \quad (5)$$

Hooke's Law is used for a low strain by

$$\epsilon = \frac{1}{E_s(\mathbf{r}_i)} \frac{F_i}{\pi R^2}. \quad (6)$$

From the above equation and Hooke's Law, we get

$$M_i^0 = \frac{1}{2\pi^2} \frac{F_i^2}{E_s(\mathbf{r}_i) R^4}, \text{ for } i \in \{1, \dots, n\}, \quad (7)$$

where R represents the cell radius. Merkel's finding [13] showed that the strain energy density decays exponentially approximately where the decay factor is given by

$$\lambda_i = \frac{E_s(\mathbf{r}_i)}{E_i}. \quad (8)$$

Here λ_i is used to represent signal attenuation ratio of elasticity modulus of substrate $E_s(\mathbf{r}_i)$ and elasticity modulus of cell E_i . We calculate the strain energy density $M_i(\mathbf{r})$ at the cell center position \mathbf{r}_i by

$$M_i(\mathbf{r}) = M_i^0 \exp\left\{-\lambda_i \frac{\|\mathbf{r} - \mathbf{r}_i\|}{R}\right\}, \text{ for } i \in \{1, \dots, n\}, \quad (9)$$

According to Vermolen and Gefen's finding [14], the energy density is a scalar number without vectorial or tensorial quantity, hence it can be summed to obtain a total strain energy density at position \mathbf{r} as follows,

$$M(\mathbf{r}) = \sum_{j=1}^n M_j(\mathbf{r}) = \sum_{j=1}^n M_j^0 \exp\left\{-\lambda_j \frac{\|\mathbf{r} - \mathbf{r}_j\|}{R}\right\}, \quad (10)$$

Thence for cell i at time t , its own sensed mechanical stimulus is represented by

$$\begin{aligned} M(\mathbf{r}_i) &= \sum_{j=1}^n M_j(\mathbf{r}_i) = \sum_{j=1}^n M_j^0 \exp\left\{-\lambda_j \frac{\|\mathbf{r}_i - \mathbf{r}_j\|}{R}\right\} \\ &= M_i^0 + \sum_{j=1, j \neq i}^n M_j^0 \exp\left\{-\lambda_j \frac{\|\mathbf{r}_i - \mathbf{r}_j\|}{R}\right\}. \end{aligned} \quad (11)$$

In Vermolen's research, the displacement direction of a cell is a linear combination of all the unit vector between this cell i and others caused by the mechanical signal. For cell i and cell j , the unit vector is $\mathbf{v}_{ij} = \frac{\mathbf{r}_i - \mathbf{r}_j}{\|\mathbf{r}_i - \mathbf{r}_j\|}$, and the total displacement of cell i during a time step Δt is parallel to

$$\mathbf{z}_i = \sum_{j=1, j \neq i}^n M_j(\mathbf{r}_i(t)) \mathbf{v}_{ij}, \quad (12)$$

where $\mathbf{r}_i(t)$ is the position of cell i at time t , and the corresponding total unit vector is $\hat{\mathbf{z}}_i = \frac{\mathbf{z}_i}{\|\mathbf{z}_i\|}$. Taking the mechanical stimulus into consideration, the total displacement over a time is calculated by

$$\mathbf{r}_i(t + \Delta t) - \mathbf{r}_i(t) = \Delta t \alpha_i M(\mathbf{r}_i) \hat{\mathbf{z}}_i, \quad (13)$$

where α_i is a parameter with dimension $[\frac{m^3}{Ns}]$ and the shear force is directed along the substrate, which acts perpendicularly to the exertion force. For viable cells, Gefen [15] achieved an expression for α_i

$$\alpha_i = \frac{\beta_i R^3}{\mu F_i}, \quad (14)$$

where β_i quantifies the mobility of the cell surface of a viable cell and μ is the cell-substrate friction coefficient, which equals 0.2 according to Gefen's simulation. Viable cells move according to the mechanical stimulus that they sense, however they are also observed to move (partly) according to random walk and hence we need to incorporate some factors for random cell movement and the magnitude of movement should be revised to

$$\mathbf{r}_i(t + \Delta t) - \mathbf{r}_i(t) = \Delta t \alpha_i M(\mathbf{r}_i) \hat{\mathbf{z}}_i + \sigma d\mathbf{W}(t), \quad (15)$$

where $d\mathbf{W}(t)$ is a vector-Wiener process and $\sigma = \sqrt{2D}$, where D represents the cell diffusion coefficient.

Gefen introduced a repulsive force into the cell contact force, which is also incorporated in the current simulations. The elastically impinging cells will generate a repulsive force to repel each other, which is determined by the invagination distance and contact radius. This invagination force will translate to the concept of energy through the computation of the amount of work. This has been worked out in [14]. Then from Hertz' contact theory the strain energy density as a result of intercellular contact is given by

$$M^{ij} = \frac{4}{15\sqrt{2}} \frac{E}{\pi} \left(\frac{h}{R}\right)^{\frac{5}{2}}, \quad (16)$$

where M^{ij} and h , respectively, denote the strain energy density produced by the elastic interaction and indentation distance between the two neighboring cells. We calculate h by

$$h = \max(2R - \|\mathbf{r}_{ij}\|, 0), \quad (17)$$

and total strain energy density $\hat{M}_i(\mathbf{r})$ for cell i by

$$\hat{M}_i(\mathbf{r}) = M(\mathbf{r}_i) - M^{ij}. \quad (18)$$

In the case of multiple cells that are in mechanical contact, the M^{ij} term has be summed over all the cells that are in mechanical contact with cell i .

During the cells migration, each cell has a life cycle that is characterized by the following stages: 1) G1, increase of RNA and ribosome during this phase the cell does not move actively; 2) S, synthesis of DNA. Further, the cell is mobile during this phase; 3) G2,

synthesis of RNA and protein. During this phase, the cell volume increases and the cell is mobile; 4) M, cell mitosis and during this phase the cell does not move actively. We will incorporate this cell proliferation process in our simulation in the future. Currently, we model cell division and death fully using stochastic principles. We assume that the probability of cell division or death obeys a simple exponential distribution and that it is only affected by the total strain energy density a cell endures, which is given by $f_{t_n}(p, t) \Delta t$ during the interval $(t_n, t_n + \Delta t)$. Here p is the probability of cell division or death per unit of time after t_n , and $f_{t_n}(p, t)$ is defined as,

$$f_{t_n}(p, t) = p \exp(-p(t - t_n)), \quad (19)$$

and hence,

$$P(t \in (t_n, t_n + \Delta t)) = \int_{t_n}^{t_n + \Delta t} f_{t_n}(p, t) dt = 1 - \exp(-p \Delta t). \quad (20)$$

To realize it in the code, we let the system randomly generate a number $\xi \sim u[0, 1]$ taken from a uniform distribution. The cell, respectively, divides or dies if and only if

$$0 \leq \xi \leq 1 - \exp(-p \Delta t), \quad (21)$$

where p stands for the rate parameter for either cell division or cell death.

3 Numerical method

Time integration for cell displacement

For solving initial value problems, the following classical methods can be listed, 1) Euler's method; 2) Modified Euler's method; 3) Runge-Kutta method; 4) Heun's method; 5) Multistep methods.

If cells just come into mechanical contact, then the derivative of the strain energy density with respect to the intercellular distance is subject to a discontinuity. Therefore we use the Euler-Maruyama method for time-integration, which is a generalization of the ordinary forward Euler method for initial value problems to stochastic differential equations. We evaluate the nonlinear parts at the previous time step. In this way, we circumvent the need of solving a nonlinear problem at each time-step. Of course, this will induce some numerical stability criteria so that the time-step can not be chosen arbitrarily large to avoid numerical instability. The differential of the displacement is generally given by

$$d\mathbf{r}_i(t) = \alpha_i M(\mathbf{r}_i) \hat{\mathbf{z}}_i dt + \sqrt{2D} d\mathbf{W}(\mathbf{t}), \quad (22)$$

where α_i denotes the rate parameter mentioned in the model section, D denotes the cell diffusion coefficient and the random variables $d\mathbf{W}(\mathbf{t})$ denotes a vector-Wiener process that

are identically distributed normal random variables with variance dt and expected value zero. Therefore the actual position of cell i at time t can be obtained from,

$$\mathbf{r}_i^t = \mathbf{r}_i^{t-1} + \Delta t \alpha_i M(\mathbf{r}_i^t) + \sqrt{2D} \Delta \mathbf{W}. \quad (23)$$

Here $\Delta \mathbf{W}$ represents a two-dimensional vector with stochastic variables from a normal distribution with zero mean and a variance of Δt .

Since the cells may collide into one another, they should not overlap each other totally. Therefore, we require their displacement to be less than one fourth of their diameter. This criterion is quantified by

$$\| \mathbf{r}_i^t - \mathbf{r}_i^{t-1} \| = \max \| \mathbf{v}_i \| \Delta t \leq \frac{R}{2}, \quad (24)$$

where R is the cell radius and \mathbf{v}_i is the equilibrium velocity of cell i . From equation (24), the largest time-step is expressed by,

$$\Delta t = \frac{R}{2 \max \| \mathbf{v}_i \|}. \quad (25)$$

This limitation of the time-step guarantees that the cells do not move too much over time-interval and do not coincide with each other. Further, numerical experiments indicate that numerical stability is also warranted if the above criterion in equation (25) is satisfied. This issue deserves some further numerical consideration in mathematical rigor.

4 The numerical simulations

4.1 Parameter Values

Currently, we use the parameter values that are listed in Table 1 for a two-dimensional modelling. We want to simulate reality as well as possible, however the majority of values are unknown, hence we have to make an educated guess and vary the parameter values based on some biological experiments as well as on the related references.

Table 1. Parameter values

Parameter	Meaning	Value	Unit
R	Cell radius	3	μm
F	Cell traction force	10	μN
Es	Substrate elasticity	5	kPa
Ec	Cell elasticity	0.5	kPa
β	Cell mobility coefficient	1	s^{-1}
μ	Friction coefficient	0.2	-
D	Cell diffusivity	0.055	$\mu m/s$
P_d	Proliferation probability rate	0.5	s^{-1}
P^D	Apoptosis probability rate	0.5	s^{-1}

4.2 Results

4.2.1 Cell migration and division

For the two-dimensional simulation, the projection of cells is supposed to be a circle on the substrate. Firstly, in Fig.1, we simulate a case of two cancer cells that approach to each other under strain energy density without random walk in a square domain with 100 micrometre side length. Once they come into contact with each other, the force reacting against invagination pushes the cells away from one another. This is modelled in equation (16) in section 2 by an additional term in the strain energy density. This eventually leads to an oscillatory behaviour and a relative equilibrium distance. Subsequently, we incorporate the random walk part in this model of which three runs are visible in Fig.2. Since the probability of random movement is quite small, the two cells still approach to each other like two ‘drunk men’ and reach to a state of relative equilibrium under attraction and repulsion.

In this model, the time for two cells meet without random walk is 265.5 seconds. As a result of random walk, the time changes a little bit, which could be shorter or longer (see Fig.3). In order to find a confidence interval with 95% confidence level, a sample for 10 runs has been chosen and the results have been listed in Table 2. The average time and standard deviation are 284.7 seconds and 23.1605, respectively. For 95% confidence level, the confidence interval is [268.3821, 301.0179].

Table 2. Time results

Number	1	2	3	4	5	6	7	8	9	10
Time(s)	298	287	260.5	286	328	286.5	282	303.5	279	236.5

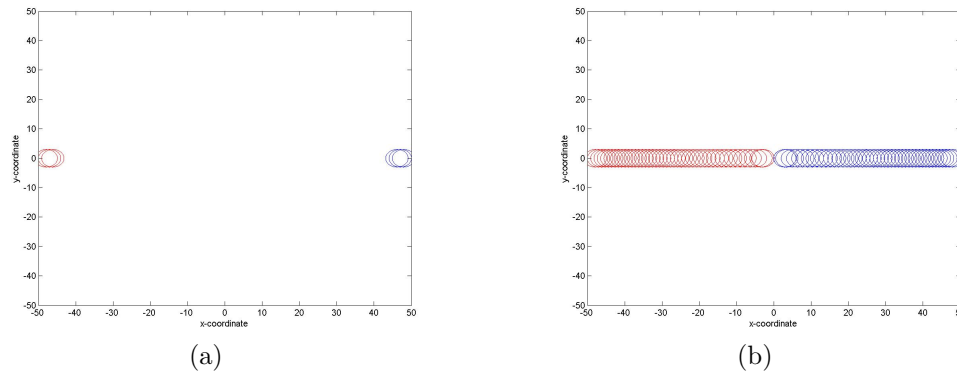


Figure 1: (a),(b).The different positions of two cells as a function of time (seconds) without stochastic perturbation of motion.

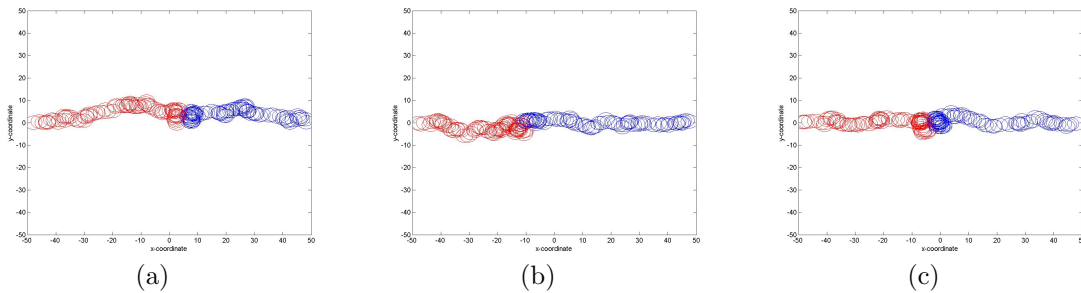


Figure 2: (a),(b),(c). Three different trajectories of two cells as a function of time (seconds) with stochastic perturbation of motion.

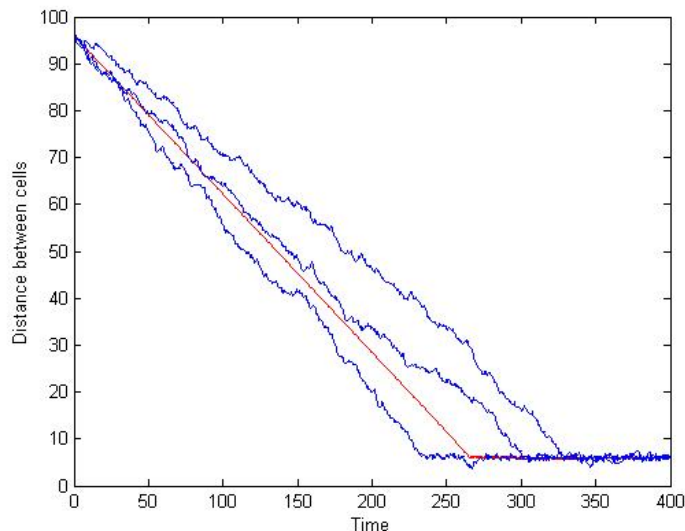


Figure 3: The red line is the distance between two cells as a function of time without stochastic perturbation of motion. The blue lines are distance between two cells for three runs as a function of time with stochastic perturbation of motion.

In this model, the probability for cell division depends on the total strain energy density that the cell senses as a result of physical contact with its neighbors. The detection threshold ε is introduced as a minimum strain energy density signal for remote cells to detect each other. Therefore, the total signal strength a cell senses should satisfy

$$M_i(\mathbf{r}) = M_i^0 \exp\left\{-\lambda_i \frac{\|\mathbf{r} - \mathbf{r}_i\|}{R}\right\} \geq \varepsilon. \quad (26)$$

Reinhart-King and his colleagues [16] found that the largest distance for a cell to detect is around $\hat{d} = 30 \mu m$ with different elasticity modulus of substrate (approximately $5 kPa$) and cell (approximately $0.5 kPa$). Hence the threshold ε is defined by

$$\varepsilon = M_i^0 \exp\left\{-\lambda_i \frac{\hat{d}}{R}\right\} \approx 4.5 * 10^{-20}. \quad (27)$$

We simulate the cell proliferation using a probability density P_d for cell division during a time-interval Δt according to different strain energy density values. We hypothesize that when a cell is in mechanical contact with six cells reaching a steady state, then it stops dividing. By equation (5) and (10), we can calculate that the value of M_i that corresponds with a cell being surrounded and just being in physical contact with six other cells such that the cell boundaries of each pair of cells coincide at one point has a value of approximately

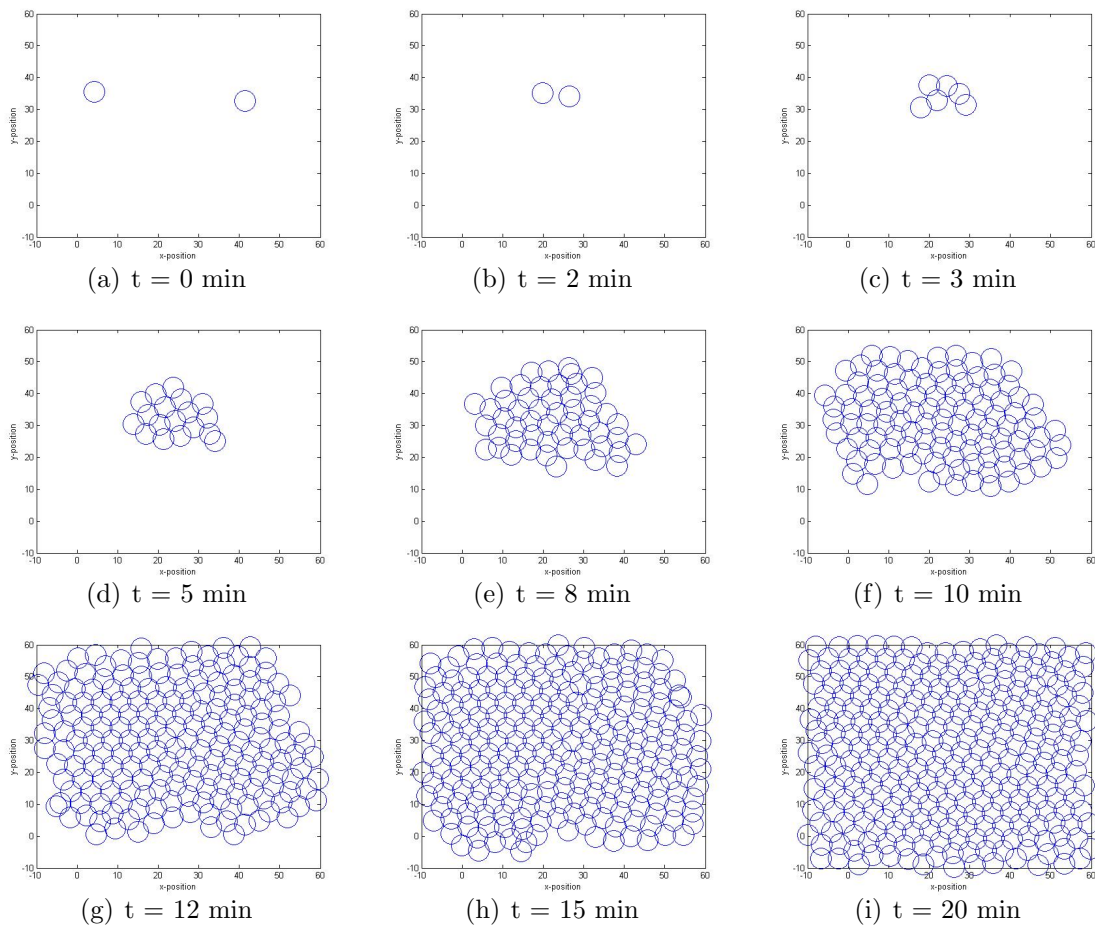


Figure 4: Snapshots of the cells migrate and division

0.225. Therefore we set,

$$P_d = \begin{cases} 0, & \text{if } 0 \leq M_i < 0.125 \\ 0.5, & \text{if } 0.125 \leq M_i < 0.225 \\ 0, & \text{if } M_i \geq 0.225 \end{cases} \quad (28)$$

The value $M_i^0 = 0.125$, so when a cell satisfies $0.125 \leq M_i < 0.225$, it will have a probability rate for division of 0.5. One cell splits into two cells and the daughter cell moves away from the mother cell gradually because of the invagination force to reach an equilibrium state. If $0 \leq M_i < 0.125$, then the probability rate for division is zero, since the cell is supposed to be overlapped a little by other cells, obtaining a repelling force. In other words, contact inhibition stops the cell division. From Fig.4, we can see that the cells almost occupy all this square region after around 20 minutes in our code. This model depicting the growth of cell colonies can be applied for tissue growth, organ development as well as tumor growth. Firstly, we model the case that a certain region can only contain a certain maximum number of cells while the boundaries cannot be penetrated. Furthermore, the probability rate for division is reduced if the cells are in mechanical contact with a large number of neighbors. Next to this reduction, the probability rate for cell death is increased if the cell is in mechanical contact with many neighbors. This will establish an equilibrium number of cells per unit area. Next we use a strict boundary limitation, so most of the cells stay in this domain and some escape away if they are under a sufficient mechanical force, which mimics the spreading of cancer cells to other tissues to various different parts of the body. This spreading could proceed by transportation via the blood circulation system or by just mechanical penetration into adjacent organs or into neighbouring parts of the body.

Furthermore, we compare the number of cells over time for various migration rates (β) and division probability rates (P_d). The results are given by Fig.5. In Fig.5a, the cell proliferation rate is significantly increased with an increase in cell migration rate and the number of cells reaches to 100 with less than the half time when $\beta = 1.5$ compared to the time needed to reach this number of cells with $\beta = 0.5$. This phenomenon happens as a result of the cells being subject to contact inhibition. The reason is that a lower migration rate makes cells remain very close to the mother cells after division, and the cells stop to divide if the glycoprotein on the cell membrane detects such information, which causes a low probability for cell division. The second picture shows that cell proliferation rate is improved slightly as the increase in cell division probability density. The model with $P_d = 0.3$ needs more time to get a certain number of cells. Assuming that the volume of the cell maximum capacity is 100, after which the cells start to die with death probability density $P^D = 0.5$. Eventually, the total number of cells oscillates around the balance of 100.

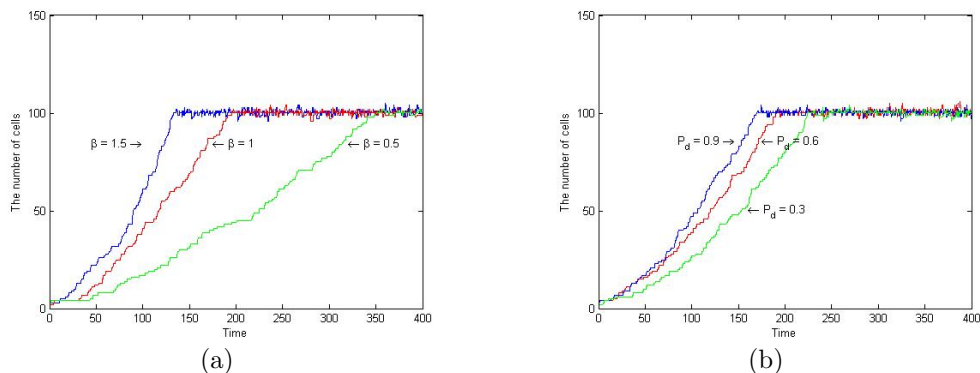


Figure 5: The number of cells as a function of time (seconds) for different values of cell motility (left) and cell division probability rates (right).

4.2.2 Tumor growth

We simulate a same square domain which is filled with epithelial cells that are able to migrate, divide and die under the strain energy density that they experience under the influence of physical contact with their neighbors. Then some epithelial cells are allowed to mutate to cancer cells which have the division rate represented by P_C . At the first stage, with sufficient oxygen and nutrition, we have $P_C \gg P_E$ (P_E denotes the division rate for epithelial cells), which causes an uncontrolled growth of the number of cancer cells. Further, the death rate of epithelial cells P_E^D become larger than P_E with limited oxygen and nutrition.

Eventually, with the low content oxygen, the tumor colony is so large that the cancer cells will spread out to other parts of the body. While some cancer cells start dying and spreading their content around towards surrounding epithelial cells so that these cells proliferate and actively migrate towards the tumor to generate new blood vessels which will migrate towards the cancer cells. Then they will supply the cancer cells with oxygen and nutrients, which makes the colony of cancer cells grow and further, as the colony grows, the cancer cells will be allowed to migrate into various neighbouring parts of the body, which causes seeding out of the tumor.

A simulation of tumor growth is shown in Fig.6, some randomly generated epithelial cells are close to each other under strain energy density and proliferate with some certain conditions. Sometimes a change happens in the genes when a cell divides and this change is called a mutation, in which a gene has been damaged, lost or copied twice. The changes in genes could be a result of one or more reasons from physical, chemical or biological factors that were mentioned in the first part. Kumar *et al.* [17] reported that the mechanical force balance can regulate a surprisingly wide range of cellular properties that are all critical to tumor genesis, including structure, motility, proliferation and differentiation. Therefore, currently we hypothesize that cell mutation is only affected by mechanical force and the

Literature study on cell-based semi-stochastic modelling for the dynamics of growth of cell colonies

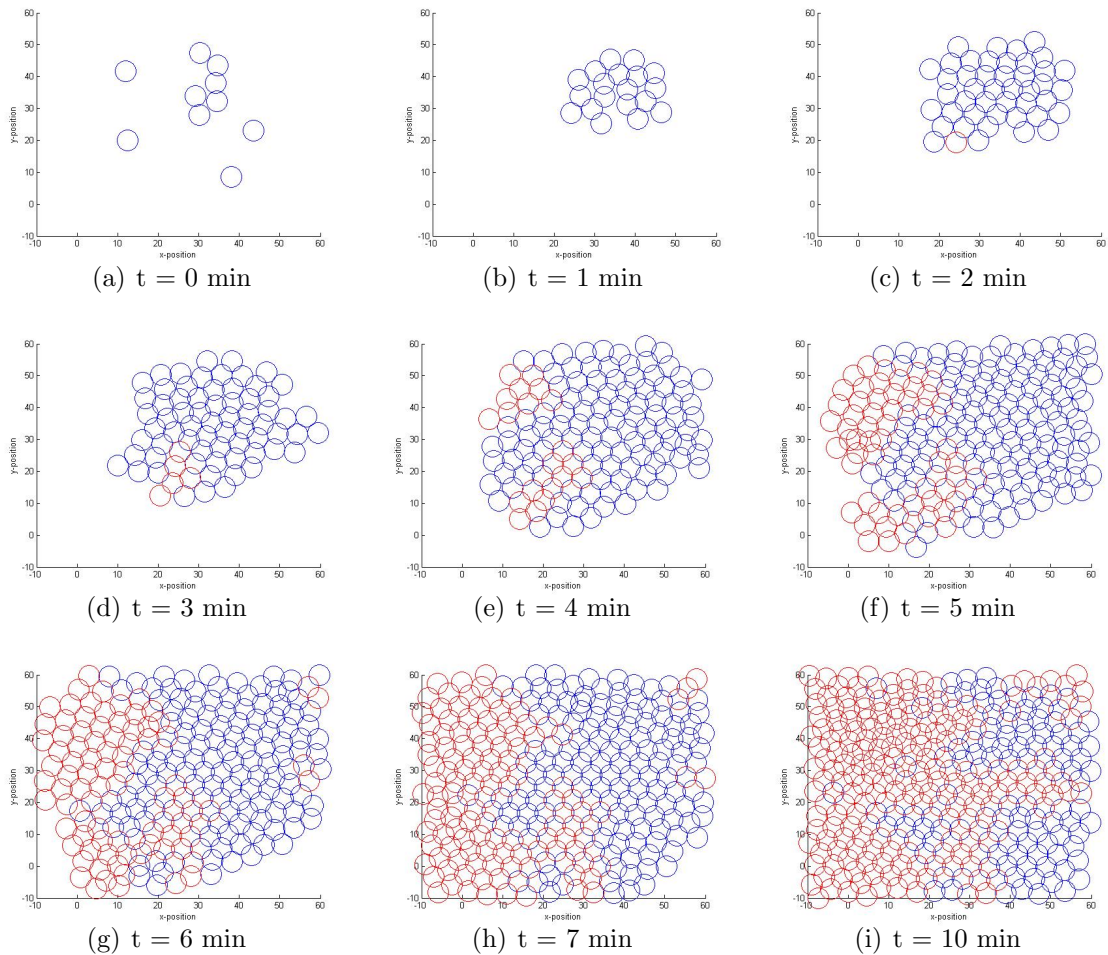


Figure 6: ‘Tumor’ growth: The arrangement of two type of cells after different times. The blue circles and red circles denote the epithelial cells and cancer cells, respectively.

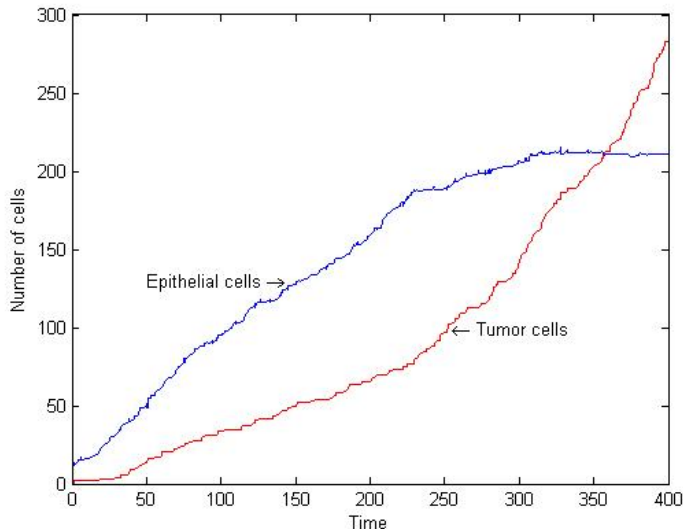


Figure 7: Changes in the number of epithelial and cancer cells versus time (seconds).

cells will mutate to cancer cells if the value $M_i > 0.30$ (see Fig. 6c). Under certain circumstances, the cancer cells start to proliferate and grow with the epithelial cells competitively. Normal cells have a certain maximum times of divisions, such as a human cell can divide a lifetime of 50 to 60 times, however, some cancer cells do not possess a maximum number of division, which leads to ‘immortal’ cells in certain circumstances. Moreover, the cancer cells have other characteristics, such as disordered cytoskeletal structure, low viscosity, reduced requirements for growth factors, *etc.*, which give cancer cells a competitive advantage for proliferation.

Finally, the number of the cancer cells exceed that of epithelial cells when they are able to grow to dangerous proportions. Fig. 7 shows the changes in the number of two types of cells as a function of time. In this picture, the cancer cells grow exponentially and its number gets higher after around 6 min. Since currently we do not have the accurate experimental data, the input values for this simulation have been chosen as hypothetical values. In future work, we will choose more accurate parameters based on related experimental results.

5 Conclusion and outlook

Modelling and simulation of cancer is still under development and we need to strengthen cooperation with other disciplines, which is beneficial for revealing the dynamics of tumor growth and death as well as to prevent cancer.

In this report, a basic cell-based model for the initial stages of cancer development is

introduced and some relevant modelling methods and results are briefly discussed. To this extent, we have three parts for simulation, 1) Two cells migrating to each other under strain energy density with and without random walk is simulated; 2) The growth of a cell colony is simulated that can be used for tissue growth, organ development and tumor growth; 3) The mutation and growth of cancer cells in the epithelial cell colony is modelled. The results show that the number of cells during the early stages of cancer development is growing exponentially. Currently, many details of the cancer cells are ignored in order to get a simple, well-tractable model for this preliminary study. We will improve our code in the future simulations as will be explained in the subsequent sections.

5.1 Improving the probability for cell division and death

In some studies, it has been found that the length of telomere DNA of cells gradually shortens as the number of divisions of a cell increases. Lindsey *et al.* [18] reported that the telomere length of skin cells becomes shorter causing cell aging and lower division rates. This phenomenon was also observed for epithelial cells, lymphocytes and hematopoietic stem cells later. Allsopp [19] observed that different individuals' fibroblasts have a stronger ability to proliferate and that the maximum number of divisions increases with increasing telomere length. Therefore the dynamic probability for cell division or death could be incorporated into the modelling to simulate initiation of cancer through an enhanced mutation rate of individual cells. In the current code, the probability rate for cell division or death has been assigned a value of 0.5 per second, however in future work we plan to make this probability rate, as well as the mutation rate, dynamic over time, which will be an innovation with respect to the existing literature. A way to do this could be the following: let N be the number of cell divisions, then we may set,

$$p_N - p_{N-1} = Cp_N(1 - p_N/p_\infty), \quad (29)$$

where C is a constant and p_N is the probability rate of cell division after N divisions per unit. The p_∞ stands for the probability for cell division after an 'infinite' number of cell divisions. As the number of cell divisions increases, the probability rates of mutation, proliferation and death will gradually converge to p_∞ .

5.2 Incorporating more factors

In this report, the strain energy density is assumed to be the only factor for cell proliferation and apoptosis. In reality, hormones, endostatin and other substances collectively influence the cell division or death. So we will incorporate oxygen content, nutrients, chemokines, *etc.*

5.3 Wound healing simulation

For the current simulation, we allow the cells to be distributed evenly in the container at the beginning to simulate the dynamic growth of the cell colonies. In future, we are going to introduce a gap at the center initially to the simulation, such as a circle, to simulate healing. Regarding closure of the epidermis, which is the top layer of skin, wound healing is very common and important for living organisms, which is achieved through migration and division of cells over the epidermis. Under damaged circumstances, the epidermal cells can have an increased mobility rate by the formation of lamellipodia such that they move towards the wound (center) at a higher pace. Furthermore, the high proliferation rate will help to form the new epidermal layer, which lays the foundation for quantification of the probability of the development of patient-disabling contractures and hypertrophic scars resulting from burns, as well as the impact of diseases related to the immune system response on a disturbed wound healing behavior. We finally note that modelling the closing rate of the epidermis and dermis is of crucial importance regarding the healing and prevention of pressure ulcers occurring on bed-bound patients [20].

5.4 Angiogenesis simulation

Since the process of tumor growth is really complicated, it is not yet fully understood how the tumor grows. Modelling is still in its early stage without unified theoretical basis. Angiogenesis plays an indispensable role in tumor growth and its spreading over different parts of the body; therefore, how to build a proper model describing the angiogenesis mechanism is going to be a complicated challenge. Innermost cancer cells of any colony are most likely to die first, since the concentrations of oxygen and nutrients to are much lower than the concentrations on the rim of the tumor. We will take the concentrations of oxygen and nutrients into account for apoptosis. Cancer cells releasing angiogenic factor activate vascular endothelial cells and thereby they promote proliferation and migration of endothelial cells. We will simulate this part combined with tumor cell dynamics and associated immune responses in future work.

5.5 A parameter variation study

Besides all these questions, all models need input parameters, which are hard to find and which vary from person to person. Therefore, it is also important to carry out a parameter variation study next to the intensive search and contact with people from medical biology. Afterwards, we could quantify the probability of tumor initiation, growth and seeding to other organs in terms of biophysical parameters, genetics and lifestyle in realistic settings and geometries.

5.6 A three-dimensional simulation

In the present study, all cells are assumed to be hemi-spherical on the two-dimensional substrate. We are going to develop mathematical cell-based models for tumor growth and wound healing in a three-dimensional framework. Microenvironment of wound healing, tumor cell growth, angiogenesis, and other immune responses can be simulated in a more realistic way with 3D models.

In order to improve the modelling efforts, a thorough basis in mathematical techniques, which are used to solve the resulting problems, will be acquired. The techniques will reside on continuum models solved by the use of finite-element strategies, as well as stochastic principles for cell proliferation, mutation, death and migration.

In general, the implementation of this research programme not only will help us to further understanding of tumor growth and wound healing, but will also provide a good framework to the prevention, diagnosis and treatment of related diseases.

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