

Cancer Modelling: Computational Models of Chemotaxis

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Fig 1: Cartoonistic cell responding to information. [4].

Introduction

Since computers have been acknowledged for their potential to generate numbers and solve lengthy calculations, algorithms have been created to solve modern problems timely.

The simulation process involves generating a discrete model to match an associated continuum model spatially, timely or a combination of the two. [1]

A discrete model is defined as a distinct, and hence countable, model which accounts for randomness whilst a continuum is the most generalised version of a mechanism or occurrence. We use continuum models to make predictions about real world phenomena.

Biology is one area simulations prove useful.

Cancer is considered one of the most serious chronic diseases with chemotherapy widely being used to combat cancer.

However, chemotherapy not only kills malignant cells but healthy cells also. In addition, very little is understood about the mathematics that govern cell migration in general.

Therefore, we aim to investigate mechanisms that govern chemotaxis through discrete simulative processes.

We investigate:

- The amount of information cells can use in their decision processes,
- The benefit of having designated leader cells combined with traditional chemotherapy.

Methods

- We simulate a lab environment through MATLAB containing a one dimensional lattice of 100 unit lengths.
- We measure lengths in units of cell diameter, or $h = 1$.
- Cells can only move at a speed of one unit length per move.
- Cells have a 60% chance of spawning
- Time is generated according to Gillipsie's stochastic simulation algorithm. In this, the smallest possible time is generated large enough for a single movement to take place. [2,3]
- Cells spawn in the middle of the lattice, around $x = 50$, and move in the x-direction.
- Cells move randomly but are subjected to biorepulsion through a density gradient to impose navigated chemotaxis.

References

- Baker, R. and Simpson, M. (2010). Correcting mean-field approximations for birth-death-movement processes. *Physical Review E*, 82(4). Majumdar, R., Sixt, M. and Parent, C. (2014). New paradigms in the establishment and maintenance of gradients during directed cell migration. *Erban, R., Chapman, J. and Maini, P. (2007). A practical guide to stochastic simulations of reaction-diffusion processes. Sonia Ong. (2020) [4].*

Results

Troubleshooting

Fig 2. depicts the unbiased simulated migration of eukaryotic cells compared with the associated continuum model over several hours.

The associated continuum model is otherwise known as the diffusion equation. [3]

The spread of cells in an unbiased setting matches closely to what we observe in the real world. This verifies the accuracy of the code for future simulations.

Cell decision processes

Fig 3. compares the cell migration for different density gradient interpretations.

On the left column, cells can only see 1 unit in front and behind them whilst cells on the right can see four units. If this didn't have an effect, we would see no difference in movement speeds and concentration.

The cells are also responding to the malignant density present. The detection of an increasing density repels the cells away from the density. This is analogous to gravity pulling us down a hill.

Biorepulsion is one mechanism that mathematicians are interested in where cells are repelled from a particular substance. This is contrasted to bioattraction.

We observe that cells can use more information than credited.

In fig 3, which has a simple hyperbolic increasing gradient, the cells move away from the malignant concentration faster when a greater distance was evaluated.

On the left column, the peak concentration of 52% occurs at $x = 38$ whilst the right simulation, who could see further, peaked 58% at $x = 32$ and is more defined; hence, testifying to the faster movement.

Effect of leader cells

Scenarios where the gradient changes direction, the effect of seeing further becomes negligible.

For the purpose of minimising variables, cells could only see one unit back and forth.

In the left column (fig 4), all cells are biased by the malignant density meanwhile only 30% of cells in the right column are biased by this. The remaining 70% are unbiased cells, like those characterised in fig 2.

These cells are referred to as 'leaders' as they undergo chemotaxis and there are no swapping conditions. Therefore, if a collision occurs, the 'followers' cannot get past and must hence follow the 'leaders' which is observed.

In the left column, due to biorepulsion, the cells tend to where the malignant density is 0. In a realistic scenario, this is unhelpful.

In the right however, with the two cell types combined, the leaders tend to the area of low malignant density and trap the followers between these peaks to attack the malignant concentration. This is highly desirable.

Applications

- Progressions of understanding in battling cancer and other diseases
- Chemotherapy synthesis and treatment
- Understanding of applied chemotaxis in cells for further research
- Predict cell migration in bioagents and other epidemics

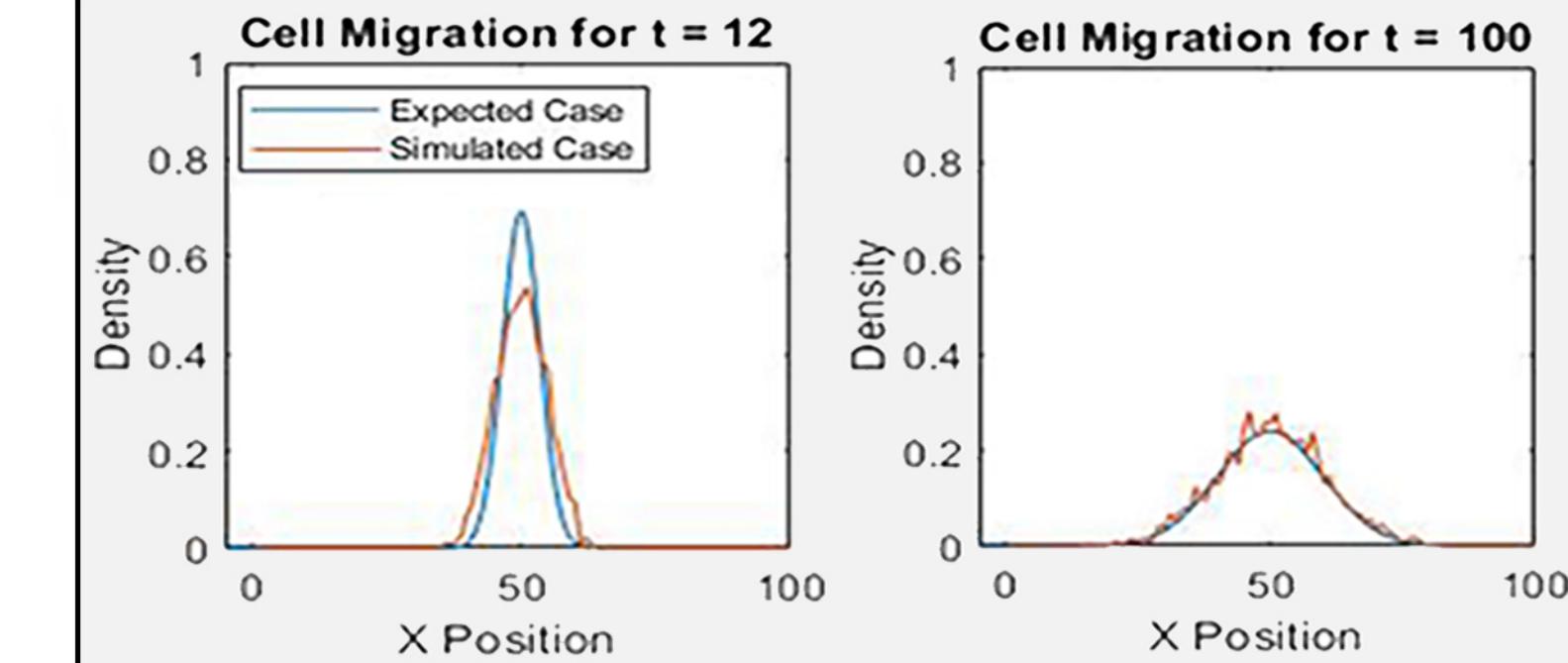


Fig 2: Unbiased simulated migration compared to the continuum model

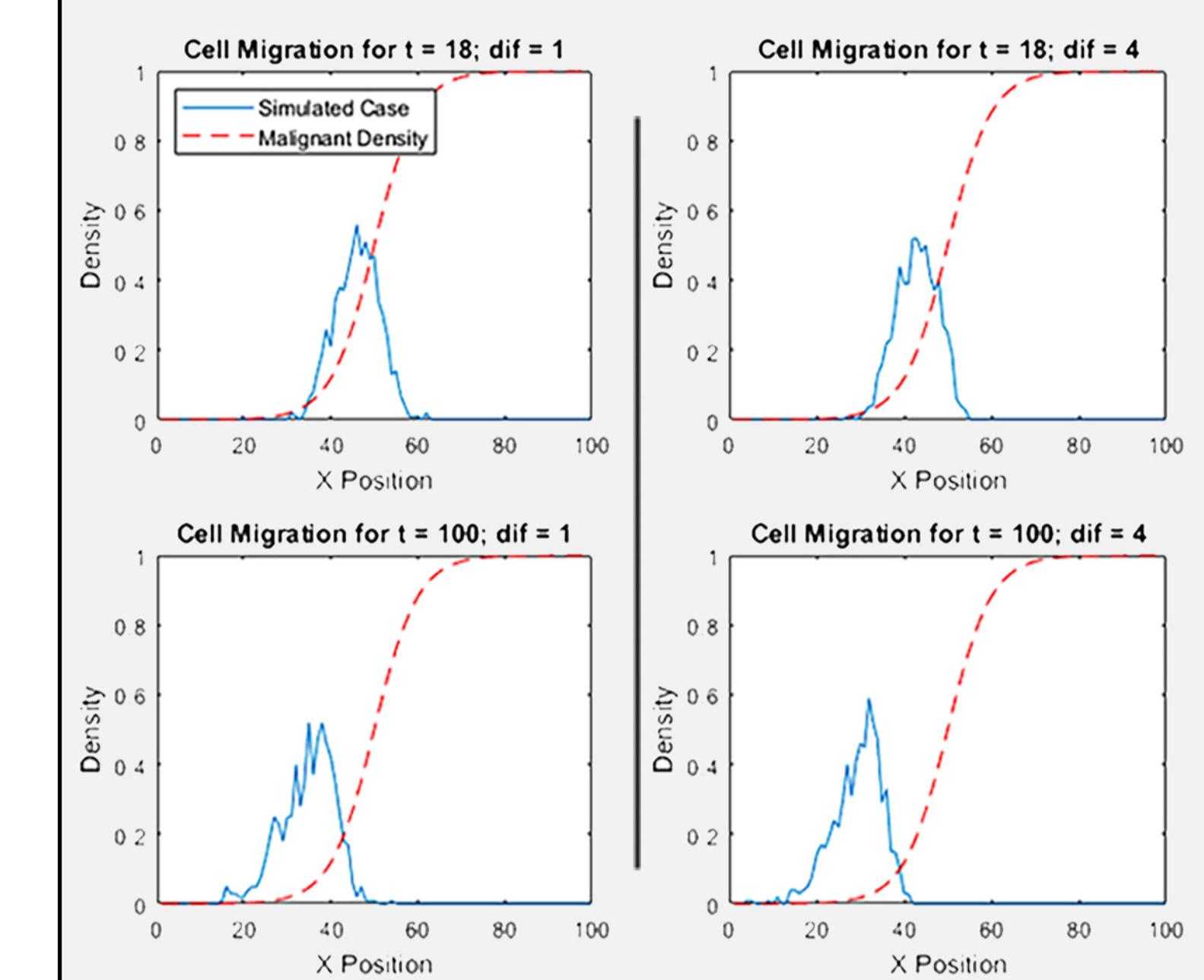


Fig 3: Comparisons of cell migration for different density gradient interpretations. On the left, cells can see a single unit in front and behind them while cells on the right column can see four units.

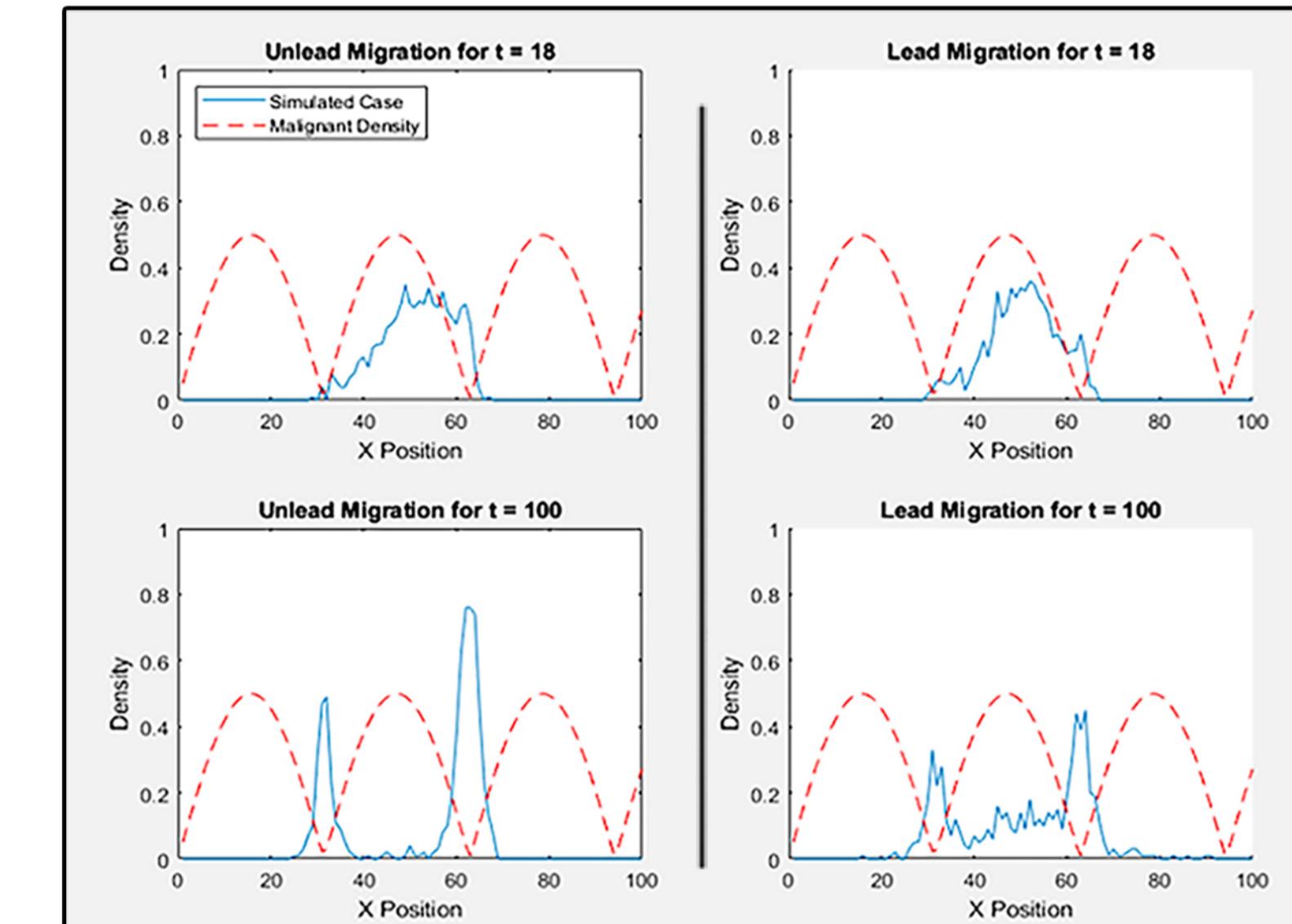


Fig 4: Comparison of cell migration without and with (respectively) leader cells in response to a malignant concentration

Conclusions

- We are able to simulate the migration of cells as we expect in the real world
- Cells can use more information than originally assumed in their decision processes
- Leader cells are beneficial when the gradient changes direction periodically