# Mean field models for cell growth processes

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## 1 Introduction

The main focus of this research was to investigate the dynamics of populations of cells using discrete simulation techniques. In the real world cells undergo several complex processes; however a reasonable simplified model has been constructed which incorporates cell movement, cell death and cell birth (or proliferation). There are numerous applications of cell growth which give rise to this study, including disease progression, tumour formation and wound healing, among others[1]. Focus is placed on populations with a sufficiently large ratio of proliferation to death to ensure that the population does not become extinct. An understanding of the dynamics of developing populations of cells will enable further explanatory and predictory analysis within the forementioned areas.

The discrete model constructed is generic, and as such can be applied to many different cell types.

## 2 Model

Simulations are conducted by first initializing a lattice with cells or 'agents'. A Gillespie algorithm is used at each timestep to select an event; movement, birth (proliferation) or death. There were two methods used when initializing cells on the lattice. The first method considered every lattice site systematically and a cell was placed in each site with a probability equal to the desired initial

average density. The second method selected a lattice site at random and deposited a cell if the site was empty, repeating this process until the desired initial desinty was met.

Both one-dimensional and two-dimensional cases are explored. In both cases time is discretized and agents have the opportunity to undergo proliferation, death or movement events at each computational step. An exclusionary process is modeled such that each site can be occupied by at most one agent at any time. If a movement or proliferation event attempts to place a cell on an occupied site, that event is aborted.

In the one-dimensional case, we construct a lattice, with spacing $\Delta$. Sites are indexed by $l$ ($l \in [1, lmax]$), and have location $x = l\Delta$. In the movement event a cell is selected at random, and given the opportunity to move in either the positive or negative $x$ direction with equal probability $1/2$. If the proliferation event is triggered a cell is chosen at random. The proliferation events employ the 'baby overboard' mechanism, a parent cell deposits a daughter cell in a neighbouring site while remaining stationary. The cell is deposited onto a neighbouring site in either the positive or negative $x$ direction with equal probability $1/2$. In the death event, lattice sites will be selected at random until a site is found to be occupied; the cell occupying this site is then terminated.

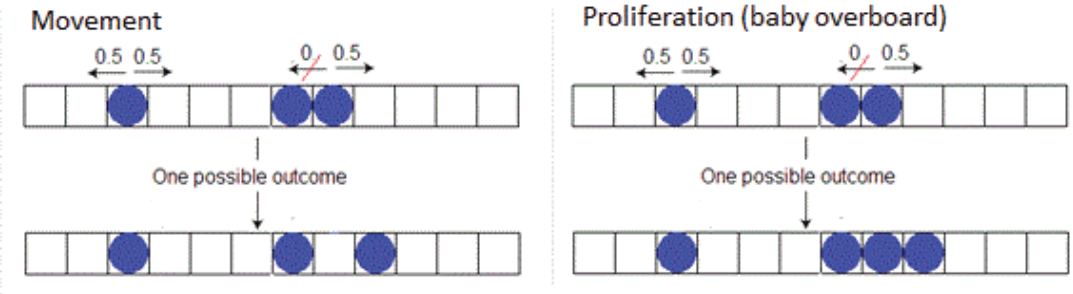


Figure 1: A diagrammatic example of both the movement and proliferation mechanisms for the one dimensional case is provided. For movement, a selected agent steps in the positive or negative $x$ direction with probability $1/2$ . For example, if the left-most agent is selected it may (successfully) move either direction with probability $1/2$. However if the rightmost agent is selected, it may only move in the positive x direction with probability $1/2$ since the other neighbouring site is occupied. For proliferation, the agent will chose direction in each case with the same probabilities as discussed for the movement example. The difference is that an additional cell is deposited rather than an original cell moving, leaving the initial lattice site occupied.

A wrapping boundary condition is imposed on the one-dimensional lattice, meaning a cell at lattice site $x = 1$ which attempts to move in the negative $x$ direction will attempt to move to $x = lmax$. Likewise a cell at site $x = lmax$ which attempts to move to the right will attempt to move to $x = 1$.

In the two-dimensional case, we construct a square lattice, with spacing $\Delta$. Sites are indexed by $i, j$; $(i \in [1, imax], j \in [1, jmax])$, and have location $x = i\Delta, j\Delta$. In the movement event a cell is selected at random, and given the opportunity to move in either the positive or negative $i$ or $j$ direction with equal probability 1/4. Proliferation follows the same mechanism as in the one-dimensional case. The cell is deposited onto a neighbouring site in either the positive or negative $i$ or $j$ direction with equal probability 1/4. The death event is unchanged from the one-dimensional case.

Similarly to the one-dimensional case, wrapping boundary conditions are imposed on all four boundaries of the two-dimensional lattice. Cells at site $x = (1, j)$ which attempt to move left will attempt to move to site $x = (imax, j)$. Cells at site $x = (imax, j)$ which attempt to move right will attempt to move to site $x = (1, j)$. Cells at site $x = (i, 1)$ which attempt to move up will attempt to move to site $x = (i, jmax)$. Cells at site $x = (i, jmax)$ which attempt to move down will attempt to move to site $x = (i, 1)$. Diagonal movement is not permitted.

Several quantities of interest are calculated using the data, including agent (single cell) density, pair density and densities of higher order groups. At pre-defined, equal time intervals the number of agents on the lattice is stored. This data is converted to a nondimensional density by dividing the agent count at each time interval by the total number of lattice sites. In order to minimise stochastic variation this data is averaged across many identically prepared realisations of the algorithm. Pair density is calculated similarly to single cell density; by counting pairs of agents (where a pair denotes agents with a certain defined separation distance) and dividing by the total number of possible paired sites on the lattice. Likewise higher order densities are calculated by counting the number of higher order groups of agents and dividing by the total number of possible groups of this size. Each of these counts encorporate the wrapping boundary described previously.

## 3 Mean field

In the study of population dynamics, the logistic differential equation desription, or 'mean field' assumption has become a canonical tool[2]. This equation is given below; where $C(t)$ represents the concentration or density of agents at time $t$, $P_p$ represents the cell proliferation (birth) rate and $P_d$

represents the death rate.

$$\frac{dC(t)}{dt} = P_p C(t)(1 - C(t)) - P_d C(t)$$

This can be solved analytically using the initial condition C(0) = C0. The solution is provided along with a plot of the result.

$$C(t) = \frac{-e^{-(P_p - P_d)t} C0(P_d - P_p)}{e^{-(P_d - P_p)t} P_p C0 + P_p - P_d - P_p C0}$$

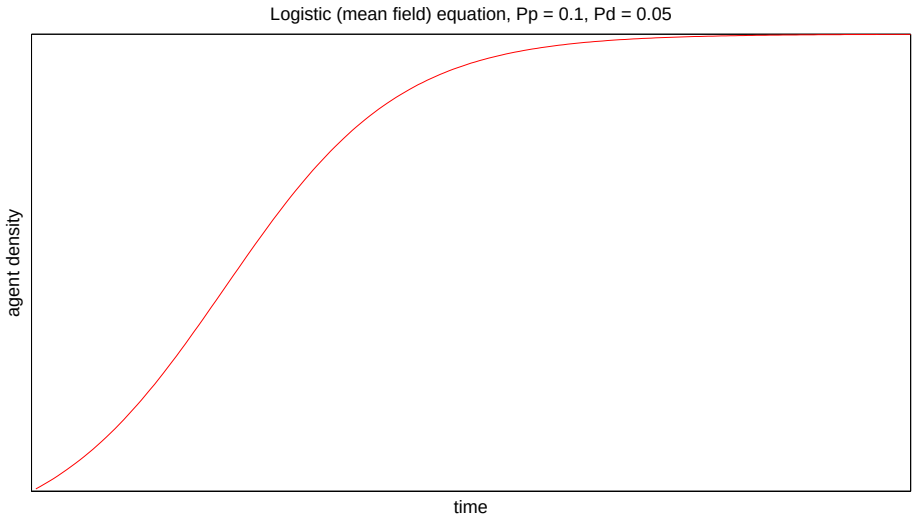


Figure 2: A plotted solution to the logistic differential equation.

The 'mean field' makes the assumption that the individual in a population are evenly dispersed. This implies that there are no spatial gradients in the system. In terms of the lattice based simulations, it assumes that the occupancy of any given lattice site is independent of the occupancy of any other lattice site. This assumption is effective in some cases, however certain parameter values give rise to cell behaviour which causes the logistic equation to break down as a predictive tool.

# 4 Results

When the ratio of cell proliferation (birth) to cell motility (movement) is increased, it can be seen through the simulation data that cells form clusters (Figure 3). This creates areas of high density and areas of low density within the system.

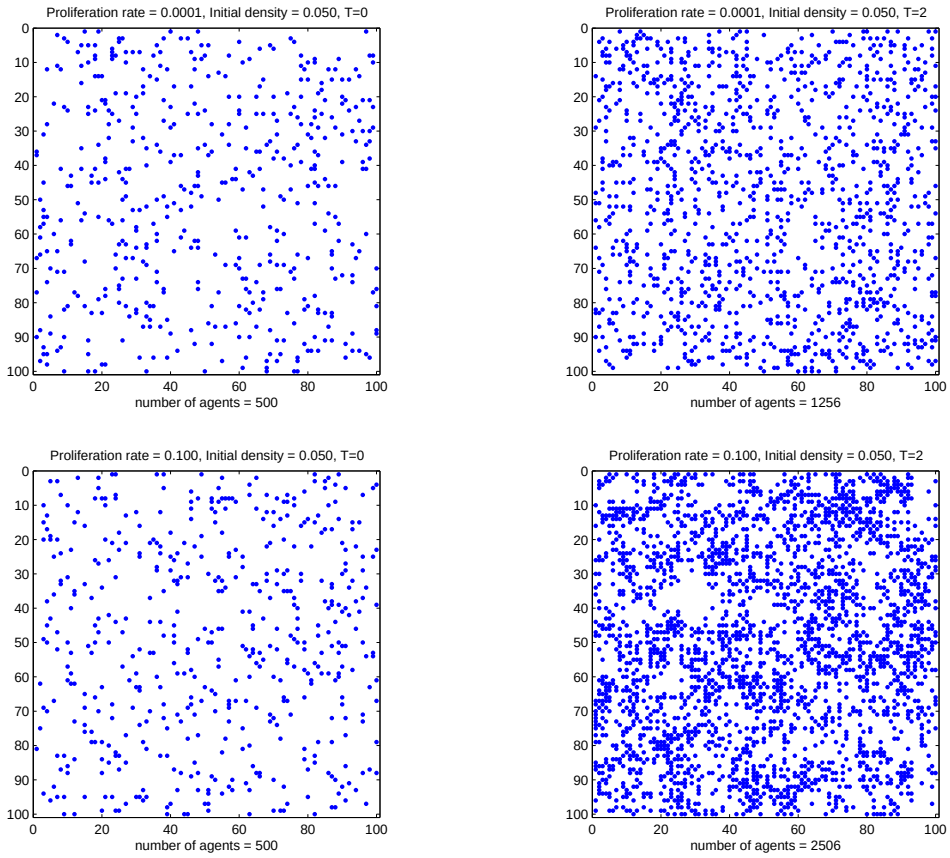


Figure 3: An increase in the ratio of proliferation to movement leads to visually apparent clustering behaviour in the simulation output.

These patchy areas of varying density violate the meanfield assumption of an evenly distributed population, and give rise to the breakdown of the logistic equation as a predictive tool. When proliferation rates are highest, the clustering effect is maximised and the simulated density deviates greatly from that which is predicted by the mean field. As the proliferation rate is reduced (and the clustering effect diminishes) the mean field becomes a far more accurate predictor (Figure 4).

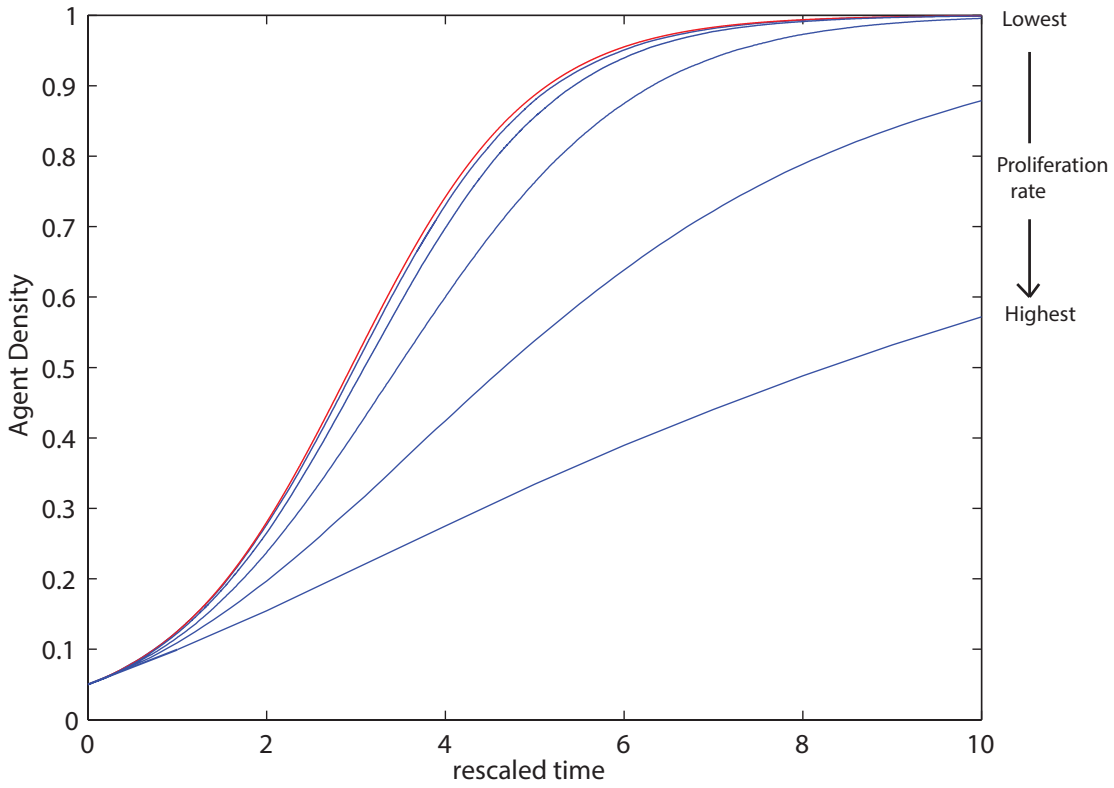


Figure 4: As the proliferation rate decreases, the deviation from the mean-field also decreases. The horizontal axis is measured in rescaled time since simulations with lower proliferation rates take a greater number of real time steps to reach a certain lattice capacity than those with higher rates. As such, time is scaled by a factor of the proliferation rate to enable comparison of simulations with differing parameter values.

A proportional cluster size distribution analysis was performed, in which the distribution of agents within certain sized clusters were compared between cases where the mean field predicted the simulated behaviour successfully, and cases where there was a large deviation. Whilst further research must be conducted to quantify the types of clusters that cause the mean field to break down, preliminary investigation indicates that the mean field is fairly robust when faced with large numbers of pairs or triplets of sites. As such it is expected that the mean field is most sensitive to the medium to large sized clusters within a population.

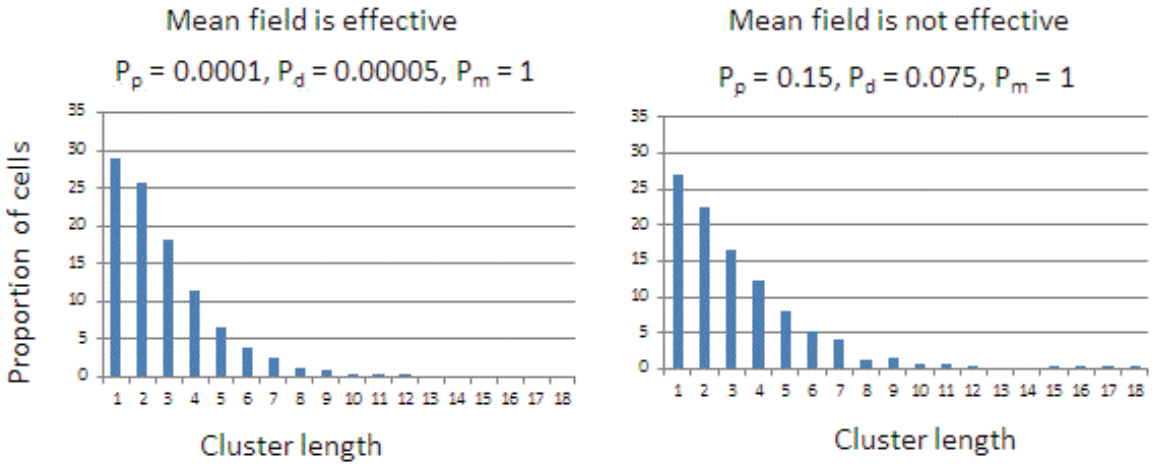


Figure 5: These figures are proportional cluster size distributions. The figure on the left corresponds to a situation in which the mean field was an effective predictor of the simulated behaviour, and the right hand side figure corresponds to a case where the simulated behaviour lead to a large deviation from the meanfield. It is clear that both cluster distributions are similar, however there are differences in the number and size of medium to large clusters which form the tail of the distribution.

Discrete simulation data reveals that the mean field is effective in some cases at predicting population dynamics of cells, however the presence of clustering within a population can lead to a breakdown of the mean field. The characterisation of clustering may prove to be a useful tool for assessing the suitability of a meanfield approach in any given situation, however further exploration of cluster distribution must be conducted before quantitative conclusions can be made.

# 5 Reference List

[1] M. J. Simpson, K. A. Landman, and B. D. Hughes, Physica A 389, 3779 (2010).

[2] R. E. Baker and M. J. Simpson, Physical Review E 02 (2010) 041905.

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