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Multi-Species Cell Simple Exclusion Process with Pair-Occupancy Correlation

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Introduction

An exclusion process is characterized by lattice-based random walk models in which agents move around and each site is occupied by at most one agent at a time (1,2). This report investigates the modelling of cell motility mechanism based on a simple exclusion process on a one-dimensional square lattice. In the derivation of partial differential equation models, independence of lattice site occupancy has often been assumed. Here, this assumption is relaxed and the effect of correlation in the occupancy of adjacent sites is considered. This effect is absent in the unbiased motility mechanism of a single cell species, as has been shown by Simpson and Baker (3). Instead, correlation effects in the unbiased motility mechanism of multiple cell species are examined.

Method

Three different models were set up and results were compared. The first model is discrete with a simulation focus on individual agent motility behaviour, and is used to generate density profiles. The second continuum model is described by a partial differential equation which encapsulates the behaviour of the entire cell population, based on the independence assumption. The third model is presented as a system of ordinary differential equations incorporating first-degree occupancy correlation.

1. Discrete Model

This model utilizes an agent-based motility rule called sequential updating method (4). At each time step, N independent random choices of agents are made sequentially, with N being the number of agents. An agent may be selected more than once, or not at all, but is selected once on average. The chosen agent is allowed to move with probability P, the motility rate. The agent may exhibit biased motility behaviour, such that it moves towards that direction with probability $(1 + a)/K$, where $-1 \leq a \leq 1$ represents the bias, and K denotes the total number of neighbours. The system is unbiased if a is equal to 0. Movement is aborted if the target site is found to be occupied.

Simulation is performed on a 2-dimensional square lattice of size 200×30. Reflecting boundary conditions are imposed on the horizontal boundaries $x = 1$ and $x = 100$, and periodic boundary conditions are imposed on the vertical boundaries $y = 1$ and $y = 30$. Occupancy rates are column-

averaged over 300 realizations to obtain a one-dimensional empirical estimate of cell density:

$$\langle C_i^{(a)} \rangle = \frac{1}{300} \sum_{k=1}^{200} \sum_{j=1}^{30} O_{i,j}^{(a)k}, \tag{1}$$

where $O_{i,j}^{(a)k}$ is an indicator function which is equal to 1 if site (i, j) is occupied by species a in the k^{th} realization, and $\langle C_i^{(a)} \rangle$ denotes the average density of species a at site i.

2. Continuum Model
A conservation equation at site s is developed as follows:

$$\frac{dC_s^{(a)}}{dt} = \frac{P^{(a)}}{K} \sum_{s' \in N(s)} \left[p(O_{s'}^{(a)}, V_s) - p(O_s^{(a)}, V_{s'}) \right], \tag{2}$$

where s' is a neighbour of s, $P^{(a)}$ denotes motility rate, K is the number of neighbours of s, O_s is the event that site s is occupied, and V_s is the event that site s is vacant. The first term represents the probability of an agent transitioning into the current site - if a particular neighbour is occupied, then the agent has $P^{(a)}/K$ probability of moving into the current site - and the second term represents the probability of transitioning out.

To derive a continuum model, the independence assumption and the law of total probability are invoked, so that $p(O_{s'}^{(a)}, V_s) = C_{s'}^{(a)}(1 - C_s)$. Then, the terms involving C and $C^{(a)}$ on the right hand side are approximated by their Taylor series expansion about s, where the distance between s and a neighbouring site s is $||s' - s|| = \Delta$. The whole equation is then divided by τ, where $\tau = t_{k+1} - t_k$ represents the size of a time step. We take the limit as Δ and τ tend to 0 whilst holding Δ^2/τ constant (5). Under the same set of boundary conditions as specified for the discrete model, the resulting model reduces to the following one-dimensional partial differential equation (for two species) since no structure is imposed on the vertical dimension:

$$\frac{\partial C^{(a)}}{\partial t} = D^{(a)} \frac{\partial}{\partial x} \left[(1 - C^{(b)}) \frac{\partial C^{(a)}}{\partial x} + C^{(a)} \frac{\partial C^{(b)}}{\delta x} \right], \tag{3}$$

where $D^{(a)} = \dfrac{P^{(a)}}{4} \lim\limits_{\Delta, \tau \to 0} \dfrac{\Delta^2}{\tau}$ is the diffusion constant.

3. ODE Model
The conservation equation for $C_s^{(a)}$ is exactly the same as (2). Without the independence assumption, evolution equations for the pair probability functions are derived based on the same principles as the conservation equation. In order to truncate the system, the Kirkwood Superposition Approximation approach (3) is used to express joint probability functions of three sites as a product of pair probability functions. Furthermore, correlation between the occupancies of non-adjacent pair sites is assumed to be negligible in order to reduce the number of evolution equations used.

The Kirkwood Superposition Approximation is given by:

$$p(O_x, O_y, O_z) = \frac{p(O_x, O_y) p(O_x, O_z) p(O_y, O_z)}{p(O_x) p(O_y) p(O_z)}. \tag{4}$$

Under the same set of boundary conditions, three ordinary differential equations are derived for each species of cell at every site s:

$$\frac{dC_s^{(a)}}{dt} = \frac{P^{(a)}}{4}\Big[C_{s-1}^{(a)} + C_{s+1}^{(a)} - 2C_s^{(a)} + p(O_s^{(a)}, O_{s+1}) + p(O_s^{(a)}, O_{s-1}) - p(O_{s-1}^{(a)}, O_s) - p(O_{s+1}^{(a)}, O_s)\Big] \tag{5}$$

$$\frac{dp(O_s^{(a)}, O_{s+1})}{dt} = \frac{P^{(a)}}{4}\left[C_{s-1}^{(a)}C_{s+1} + \frac{p(O_s^{(a)}, O_{s+1})p(O_s^{(a)}, O_{s-1})}{C_s^{(a)}} - p(O_s^{(a)}, O_{s+1}) - \frac{p(O_s, O_{s+1})p(O_{s-1}^{(a)}, O_s)}{C_s}\right] + \frac{P}{4}\left[C_s^{(a)}C_{s+2} - p(O_s^{(a)}, O_{s+1})\right] \tag{6}$$

$$\frac{dp(O_s^{(a)}, O_{s-1})}{dt} = \frac{P^{(a)}}{4}\left[C_{s+1}^{(a)}C_{s-1} + \frac{p(O_s^{(a)}, O_{s-1})p(O_s^{(a)}, O_{s+1})}{C_s^{(a)}} - p(O_s^{(a)}, O_{s-1}) - \frac{p(O_s, O_{s-1})p(O_{s+1}^{(a)}, O_s)}{C_s}\right] + \frac{P}{4}\left[C_s^{(a)}C_{s-2} - p(O_s^{(a)}, O_{s-1})\right] \tag{7}$$

where P denotes the motility rate of the entire population, obtained as a weighted average of the motility rates of all species.

Results

In the simulation, the initial condition is such that the sites where $81 \leq x \leq 100$ are fully occupied by species A, and the sites where $101 \leq x \leq 120$ are fully occupied by species B.

Discussion

In both cases, the three models produce almost identical results up to $t = 100$. This may be because the centre region has high densities, which allow for fewer cell movements, and hence is subject to less effect from correlation. Densities in outer regions are low, and correlation effects are weaker. But as cells propagate outwards and densities in the centre sites decrease, more movements are allowed and correlation effects begin to assume significance. As the system evolves through time, the aggregated correlation effect is stronger. At $t = 1000$, the ODE model clearly provides a better match to the discrete simulation results. The match is more accurate for both species if they have the same motility rate. When motility rates differ, the solution is almost exact for the less motile species, but less precise for the other.

Since the ODE solution does not provide an exact match, it is clear that correlation between the occupancies of non-adjacent sites, though weaker, exists. The discrepancy is most prominent at the peaks, suggesting that correlation effects are greater in high-density regions. Greater precision will be achieved if higher degree correlation was incorporated, but would at the same time produce a much more complicated ODE system comprised of considerably more equations.

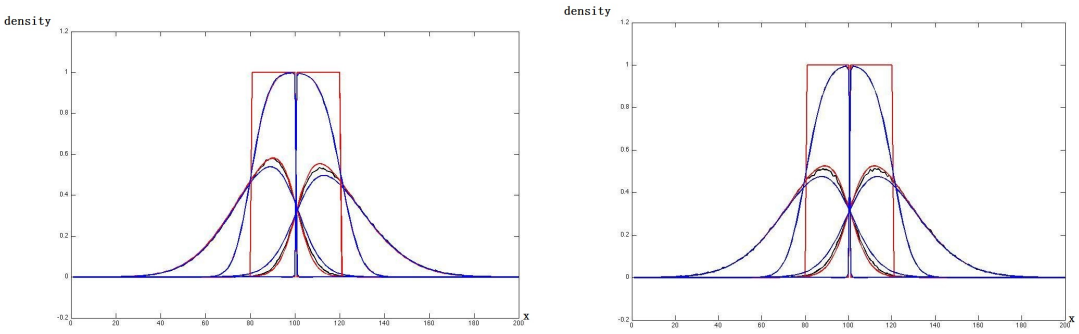

Figure 1: Left: $P^{(a)} = 0.75$, $P^{(b)} = 1$. The state of the system at $t = 100$ and $t = 1000$ are shown along with the initial condition. The horizontal axis denotes the sites x, and the vertical axis denotes cell density at each site. The discrete simulation results are displayed in black, PDE model in blue and ODE model in red. Right: $P^{(a)} = 1$, $P^{(b)} = 1$. The state of the system at $t = 100$ and $t = 1000$ is shown along with the initial condition. Discrete results are displayed in black, PDE model in blue and ODE model in red.

A challenge that still remains is that the ODE system encounters numerical errors if the difference between the cell motilities were too great or if the system had run for a longer time span, such that Matlab's stiff ODE solvers would encounter matrices that are close to being singular. This results in solutions that either diverge at the peaks or turn negative at certain locations.

AMSI Experience

This scholarship has enabled me to apply the mathematical knowledge I have learnt over the past three years to a problem in biology. My research experience helped solidify my understanding of differential equations and their derivation, enhance my computer-based problem-solving skills and practice my report-writing and presentation skills. Most importantly, I learnt that it is not at all easy and quick to obtain sound results in research, and that it is usual to get stuck for a long time before a spark of inspiration comes by to produce a minor breakthrough. I caught a glimpse of what professional research life is like and saw if my passion really lies within research and if I would really want to pursue a PhD degree.

The Big Day In gave me a valuable opportunity to present my findings and share my thoughts with other brilliant mathematics students from all across Australia. It was fascinating to listen to the various maths topics, many of which I have never encountered before, and to learn about what sort of questions in these fields in which mathematicians currently take an interest. I would like to thank my supervisors, Professors Barry Hughes and Kerry Landman, for the help they provided during my six-week research, and CSIRO and AMSI for their generous support.

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