

Multi-level behaviours in agent-based simulation: colonic crypt cell populations

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Agent-based modelling and simulation is now beginning to establish itself as a suitable technique for studying biological systems. However, a major issue in using agent-based simulations to study complex systems such as those in Systems Biology is the fact that simulations are ‘opaque’. While we have knowledge of individuals’ behaviour through agent rules and have techniques for evaluating global behaviour by aggregating the states of individuals, methods for identifying the interactive mechanisms giving rise to this global behaviour are lacking. Formulating precise hypotheses about these multi-level behaviours is also difficult without an established formalism for describing them. The complex event formalism allows relationships between agent-rule-generated events to be defined so that behaviours at different levels of abstraction

to be described. Complex event types define categories of these behaviours, which can then be detected in simulation, giving us computational method for distinguishing between alternative interactive mechanisms underlying a higher level behaviour. We apply the complex event formalism to an agent-based model of cell populations in the colonic crypt and demonstrate how competition and selection events can be identified in simulation at both the individual and clonal level, allowing us to computationally test hypotheses about the interactive mechanisms underlying a clone's success.

1 Introduction

Biological systems are complex adaptive systems (CAS) where a great number of entities interact to give rise to system-level behaviours and processes. These systems are inherently difficult to study because they exhibit polymorphism, context dependency, evolution, reprogrammability, emergence, non-linearity, heterogeneity, hierarchy and complexity [7], [13], characteristics shared by most complex systems. Agent-based modelling and simulation (ABMS) is now a fairly well-established technique for studying such complex systems [16] but it has only recently begun to be seriously adopted in Systems Biology e.g. [17]. When used to study biological systems, ABMS allows certain hypotheses about individual-level behaviour (e.g. at the level of cells) to be validated and refined, since the overall system behaviour observed in simulation can then be compared with that observed in the real system. While a correspondence does not verify a hypothesis, it does show that it is valid and able to generate the expected behaviour. ABMS is therefore seen as a way of performing 'thought experiments' [12]. Rules are defined at the agent level, while the behaviour of the whole system is typically represented by a macro-state variable that aggregates the states of all the agents in some way; this macro-state variable is then tracked through time.

A major problem with this approach is the loss of structure when states are aggregated e.g. no information about spatial locality is retained. This means that we are unable to identify the mechanisms (the actual interactive patterns between agents) that give rise to a particular global behaviour. For this reason, simulations are usually visualised, allowing the human experimenter to observe visually the interactions taking place through time. Hypotheses about such interactions are then formulated in natural language and hence vague e.g. 'the cells cooperate to survive'. In this paper, we seek to address this problem by introducing a formalism that allows such hypotheses to be expressed precisely in terms of the agent model. Once expressed formally, we can then identify the particular interactive mechanisms or classes of mechanisms in an agent-based simulation, giving us a computational method for testing such hypotheses. We illustrate this using ABMS of cell populations in the colonic crypt.

The section that follows (Section 2) briefly introduces the complex event formalism. Section 3 describes the agent-based model of colonic crypt cell populations. Section 4 formulates hypotheses about clonal level behaviours using the complex event formalism and discusses the results from detecting these behaviours in simulations. The final section (Section 5) concludes the summarises

and concludes the paper.

2 Compositionality and Complex events

In this section, we briefly introduce the complex event formalism, which allows multi-level behaviours in agent-based simulations to be described. These behaviours are sometimes called ‘emergent’ because they have organisational properties that are not explicitly specified in the agent rules (reviews of theories of emergence can be found in [6], [5] and [1]). A more detailed account of the formalism and its relevance to current theories of emergence can be found in [3].

There are four central ideas behind the formalism, all relating to way that properties (in this case behaviours) can be located in a system or simulation.

- Every behaviour in a system can be described by events (state changes) located in an n-dimensional (hyper)space. For the lifetime of the system or simulation, events can be located in this space by specifying the coordinates in each of the dimensions. The coordinate system used to specify the location can be global (from a whole system point of view) or local (where locations are in relation to a particular constituent *within* the system).¹
- If two macro-properties consist of constituents of the same types and constituents of the same type have the same configuration with respect to each other in the two properties, we can say the two properties are of the same type.
- We can describe **regions** as well as point locations in a system or subsystem space using propositional statements about the location in the system/simulation’s various dimensions. For example, in a system with only time and identity represented, (before 3, 4) stands for all the states or state transitions that occur in component 4 before time step 3.
- Higher level properties can be composed by defining organisational relationships between their constituents i.e. their **configuration**. This idea is generalisable to any dimension.

2.1 Complex events and simple events

In an agent-based simulation, every event is the result of an agent rule being applied; we call these simple events. Simple events can be defined at various levels of abstraction, depending on which of the components (e.g. variables, agents²) affected by the rule application we are concerned with. For example, a

¹For example, if the global coordinate (12, 1, 4, 2) represents the location of a state transition in the 12th time step (first tuple item holds time), located in coordinate (1, 4) of physical space (second and third tuple items hold space) in component with ID 2 (final tuple item holds component identity); the equivalent coordinate using a local coordinate system defined with respect to component 2 at time step 11 in the same spatial location would be (1, 0, 0, 0).

²Agents can be treated as complex variables.

rule that causes state changes in components a , b and c can cause simple events $(q_a, q_b, q_c) \rightarrow (q'_a, q'_b, q'_c)$, $(q_a, q_b) \rightarrow (q'_a, q'_b)$..., $q_a \rightarrow q'_a$...etc. We call this the scope of the event. Two simple events e_1 and e_2 in a system are said to be of the same type if (a) e_1 and e_2 result from the same agent rule and (b) the scope of e_1 is identical to the scope of e_2 i.e. for every component in which a state change occurs in e_1 , there is a component of the same type in which the same type of state change occurs in e_2 ³.

A complex event CE is defined as either a simple event SE or two complex events linked by \bowtie :

$$CE :: SE \mid CE_1 \bowtie CE_2 \quad (1)$$

\bowtie denotes the fact that CE_2 satisfies a set of location constraints with respect to CE_1 . Conceptually, complex events are a configuration of simple events where each component event can be located in a region or point in a hyperspace that includes time, physical space and any other dimensions. The set of location constraints can be represented as a coloured multi-graph, where the node colours stand for event types and the edge colours for different relationship types (the location constraints) existing between the events [4].

2.2 Complex event types for multi-level behaviour

We have already introduced the idea that events can be typed in our discussion of simple events. We now extend this to complex events. Two complex events CE_1 and CE_2 are said to be of the same type if, for each constituent event e_1 in CE_1 there is exactly one event e_2 in CE_2 satisfying the same location constraints, and e_1 and e_2 are events of the same type. To specify a complex event type therefore, we need to specify the types for each of the constituent events and the location constraints that hold between them.

Complex event types can differ in specificity. A fully determined complex event type CET_{Full} is defined as one whose constituent events are in a fully determined configuration i.e. given the global location of one constituent event in the complex event, it is possible to work out the precise location of every other constituent event. A partially determined complex event type CET_{Part} is an event type with a partially determined configuration and therefore defines a set of complex events with fully determined configurations.

$$CET_{Part} = \{CET_{Full}\} \quad (2)$$

The dimensions in which configurations are not fully specified lower the resolution of the complex event, with weaker constraints (greater ranges of possible values) implying a lower resolution in that dimension. More generally, the greater the number of complex event types with fully determined configurations that a complex event type contains, the lower its resolution.

³See [9] for a formal definition of types

Having briefly outlined the complex event formalism, we now introduce the agent-based model of colonic crypt cell populations used to demonstrate its application.

3 Cell population model

In this section, we describe the agent-based model used for simulations of colonic crypt cell populations. Section 3.1 gives the biological background that forms the basis of the model while Section 3.2 gives the agent rules.

3.1 Biological background

The colon is made up of villi, which are finger-like structures each made up of ~300 cells - 15 cells in diameter, 20 cells from the closed bottom (colonic crypt) to the villus tip [14]. In a colonic crypt, cells divide, differentiate and migrate up the crypt. Stem cells reside at the bottom of the crypt and typically divide asymmetrically to give one transit cell and one stem cell. Transit cells have the ability to divide a limited number of times (usually around 3 times) after which they undergo terminal differentiation. Fully differentiated cells are removed from the luminal surface by programmed cell death (apoptosis).

Cells can take two to seven days to migrate from the site of their final division to the villus tip [18] and stem cells have cycle times ranging from 10 to 14 hours (consisting of G_1 , S , DNA repair, G_2 , and M phases) after which they enter a resting phase (G_0) of one or two days before they divide again [2].

3.2 Rules for cell agents

In our simulations, a single time step represents an hour of real time. Given what we know about the durations of cell division and migratory processes (as outlined in Section 3.1), Table 1 summarises the event timings used in the model. Where a range is given, a duration within the range is randomly selected.

Table 1: Durations for cell cycle stages and migration

Event	Real time duration (range)	Simulation time steps
G_0 (Resting)	24h-48h	24-48
G_1 Phase	1h-5h	1-5
S Phase	8h	8
Repairing DNA	1h-5h	1-5
G_2 Phase and M Phase	1h	1
Migration	48h-168h	48-168

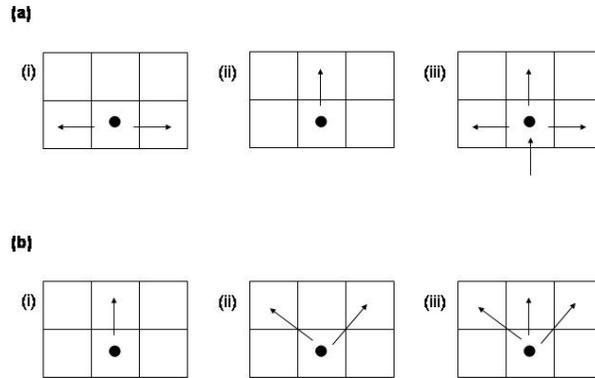


Figure 1: (a) Possible target locations for insertion when a new cell agent is produced from cell division. The arrows represent the possible locations for insertion if the parent cell is located in the position occupied by the black dot. (i) The new cell first attempts to insert itself in each of the adjacent positions (the order is determined randomly). (ii) If the two adjacent locations are both occupied, the new cell tries the location directly above the parent cell. (iii) If all these positions are occupied, it randomly selects one of the occupied positions (including the parent cells) and attempts to oust the cell currently occupying that position. The parent cell itself might be ousted if its position is randomly selected by the newly produced cell. If the cell fails to oust the existing cell, it fails to be inserted and ‘dies’. (b) Migration. (i) The cell agent first tries to move into the position directly above its current location. (ii) If the position directly above is occupied, it tries each of the positions adjacent to this (the order is determined randomly). (iii) If all these locations are occupied, the cell randomly selects one of the occupied positions and tries to oust the cell currently occupying that position. If it fails, the cell remains where it is.

When a cell agent divides, it produces an additional cell agent which needs to be inserted at a location close to the parent cell. If all the locations in the parent cell’s neighbourhood are occupied, the new cell agent randomly selects a location that it attempts to occupy by ‘killing’ the cell currently occupying the location (this might be the parent cell). Similarly, when a cell attempts to migrate upwards, it can ‘kill’ a cell occupying the space it is trying to move into (see Figure 1). The likelihood of a cell agent ousting another is a function of its fitness *relative* to its competitor’s so that two cells with equal fitnesses have the same probability of ‘losing’ in a competition (in the simulations presented here, all cells have equal fitnesses). After three divisions, transit cells differentiate and can no longer divide, although they continue to migrate before eventually being lost when they reach the villus tip.

The model is used to simulate a single villus with maximum capacity 300

cells i.e. 300 grid locations (15 cells in diameter, 20 cells from bottom to top). Initially, the villus only has 6 stem cells in the crypt but is then populated through division and migration of cells. Free locations in the crypt base are filled with new stem cells at each time step to model their continuous replenishment.

4 Identifying competition and selection events in simulation

Biological systems tend to be hierarchical [8], [10]. This means that the behaviour of a system can be observed and analysed at different levels of abstraction. In this paper, we consider relationships between clonal level behaviour and overall clone population dynamics.

4.1 Clone population dynamics

Ten 1000-time-step simulations were run based on the model. For each simulation, the clonal populations were tracked through time, with several types of dynamics being observed (see Appendix 1). In some cases, one or two clones were significantly more successful than the others. (This result in itself has interesting implications for the Systems Biology of Cancer, since it means that tumours may develop even when their cells have no intrinsic selective advantage over normal cells, supporting the hypothesis that cancer is often a systems disease [11]).

We try to validate two hypotheses about the strategies clones adopt to when they are expanding. We consider the significance of clustering and a particular ‘motif’ of behaviour that it enables. The section that follows demonstrates how complex event types can be used to identify these.

4.2 Complex event types for clustering structure and clonal behaviour

We wish to test two hypotheses:

1. Clustering is common in successful clones (or when clones are successful⁴) since members of the clone protect one another.
2. Move events by members of a clone can lead to clonal expansion when a division or move by another clone member means the unoccupied previous location is filled by another clone member (see Figure 2). We hypothesise that this pattern of behaviour is more common in successful clones/when clones are successful.

These can be reformulated in terms of complex events so that they can be tested computationally during simulation. We begin by defining the following simple event types, each with a particular scope:

⁴As mentioned above, clone success often varies throughout the simulation.

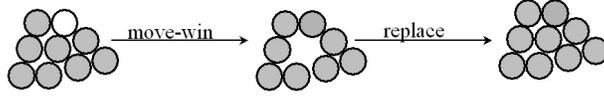


Figure 2: move-win-replace complex event type. First, a cell belonging to a clone cluster moves into a new location and ousts a cell belonging to another clone. Then the cell's previous location is occupied by another cell in the clone cluster, allowing the cluster to expand.

- *ma*: cell attempts to move into a new location. The scope consists of (i) *S*, the source location; (ii) *T*, the target location; and (iii) *M*, the moving agent.
- *ia*: cell attempts to occupy a location currently occupied by another cell. The scope consists of (i) *I*, the cell attempting to occupy the location; and (ii) *O*, the cell currently occupying the location.
- *cp*: competition between two cells. The scope consists of (i) *W*, the cell that wins in the competition; and (ii) *L*, the cell that loses in the competition.
- *mv*: cell moves to a new location. The scope consists of (i) *S*, the source location; (ii) *T*, the target location; and (iii) *M*, the moving agent.
- *dv*: cell divides to give a new cell. The scope consists of (i) *P*, the parent cell and (ii) *C*, the child.
- *in*: a newly created cell is inserted into a location. The scope consists of (i) *N*, the new cell and (ii) *T*, the target location.

Within-clone competition Clone clustering can be determined by the degree of within-clone competition, which corresponds to the event type:

$$wcc :: cp(W.cloneID = L.cloneID) \quad (3)$$

This is a sub-type of the *compete* event type.

Move-win-replace A strategy that is believed to be successful for expanding a clone cluster is where a cells first replaces a cell from another clone and then has its own previous location filled by a member of its own clone. This corresponds to the complex event type (see Figure 2):

$$mwr :: ma1 \bowtie_A ia \bowtie_B cp \bowtie_C mv1(\bowtie_D ma2 \bowtie_E mv2 || \bowtie_F dv1 \bowtie_G in)$$

where

- $\bowtie_A :: (; [T_{ma1} = O.loc, M_{ma1} = I])$, i.e.the target location T_{ma1} of the move attempt $ma1$ is the same as the occupant O 's location in the invade attempt ia and the moving agent M_{ma1} is the invader I .
- $\bowtie_B :: (; [I = W])$, i.e. the invader I in invade attempt ia is the winner W in the compete event cp .

- $\bowtie_C:: (; [L.loc = T_{mv1}, W = M_{mv1}])$, i.e. the loser L 's location is the target location T_{mv1} of the move event $m1$ and the winner W in the compete event cp is the moving agent M_{m1} in the move event $mv1$.move is winner.
- $\bowtie_D:: (; [S_{mv1} = T_{ma2}, M_{mv1}.cloneID = M_{ma2}.cloneID, M_{m1}! = M_{ma2}])$, i.e. the target location T_{m1} of the second move attempt $ma2$ is the same as the source location S_{m1} of the first move event $m1$, the moving agents M_{m1} and M_{ma2} belong to the same clone but are different individuals.
- $\bowtie_E:: (; [T_{ma2} = T_{mv2}, M_{ma2} = M_{mv2}])$, i.e. the target T_{ma2} of the move attempt $ma2$ is the same as the target T_{mv2} of the actual move $mv2$ and the moving agent is the same individual.
- $\bowtie_F:: (; [M_{mv1}.cloneID = C_{dv}, M_{mv1}! = C_{dv}])$, i.e. the moving agent M_{mv1} and the newly created child agent C_{dv} belong to the same clone but are different individuals.
- $\bowtie_G:: (; [C_{dv} = N_{in}, S_{mv1} = T_{in}])$, i.e. the target T_{in} of the insert is the same as the source location S_{mv1} of the move $mv1$ and the new cell from division is the same cell as the new cell to be inserted.

(; is the next event operator.⁵)

The complex event mw stands for the complex event where a cell moves into a space previously occupied by a cell from another clone:

$$mw :: ma1 \bowtie_A ia \bowtie_B cp \bowtie_C mv$$

We can now re-formulate our two hypotheses in complex event terms:

1. When a clone is successful (has a greater number of individuals compared to other clones), it will have (proportionally) more within-clone competition wcc events (relative to the overall number of competition events for the clone), indicating that more of its cells exist in a cluster.
2. A successful clone will have (proportionally) more move-win-replace mw events (relative to the number of mw events for the clone).

Since it is highly contested whether the classical model of causality holds for complex systems, we do not make reference to it in our hypotheses, nor do we assume it.

4.3 Results and discussion

To validate the two hypotheses, we first considered clonal success at 100 time-step intervals. Clonal success is represented by the average number of individuals in each clone μ_X over a time interval ρ divided by the overall average number of individuals μ_{ALL} i.e. for each clone X :

⁵In this particular example, we are assuming the simulation is a discrete event simulation so that each step does not necessarily have to represent the same unit of time.

$$success_{\rho} = \frac{\mu_X}{\mu_{ALL}}, \quad (4)$$

where

$$\mu_X = \frac{(v_X t_m + v_X t_{m+1} \dots + v_X t_n)}{n - m},$$

$$\mu_{ALL} = \frac{\sum(\mu_{X1}, \dots, \mu_{X\sigma})}{\sigma},$$

$\rho = n - m$ is time interval (in the analysis presented here, $\rho = 100$), $v_X t_i$ is the number of individuals in X at time step i , and σ is the number of clones. $success_{\rho}$ therefore indicates each clone's success relative to the others in a given simulation. The proportions of wcc events (relative to $success_{\rho}$) and mwr events (relative to $success_{\rho}$) were then calculated for these intervals. This was done for each simulation and then for the whole set of simulations. Results of clones that became extinct were omitted after the time interval in which they became extinct.

The respective relationships between clonal success and wcc/mwr were evaluated by calculating the correlation coefficient r between clonal success and wcc/mwr occurrence (see hypotheses above). A t-test was then conducted for each of these to test their significance. For the single simulation analyses,

Since each simulation had 1000 time steps and 6 clones, the total number of data items considered was $N \leq 60$ for the single simulation analyses (less if there were extinctions) and 1200 for the aggregated analysis. The results are shown in Table 2.

Table 2: Correlations between clonal success and wcc events/ mwr events. Accuracy 3 decimal places. The p values do not assume directionality and significance (sig.) is determined based on a 95% confidence interval.

Sim.	N	df	r_{wcc}	t_{wcc}	p_{wcc}	r_{mwr}	t_{mwr}	p_{mwr}
1	60	58	0.277	2.196	0.032 (sig.)	-0.386	-3.183	0.002 (sig.)
2	44	42	0.301	2.043	0.047 (sig.)	-0.402	-2.845	0.007 (sig.)
3	37	35	0.212	1.285	0.207	-0.286	-1.767	0.086
4	46	44	0.254	1.739	0.089	-0.378	-2.712	0.010
5	52	50	0.242	1.763	0.084	-0.474	-3.807	0.000 (sig.)
6	60	58	0.298	2.378	0.021 (sig.)	-0.307	-2.458	0.017 (sig.)
7	43	41	0.270	1.796	0.080	-0.477	-3.479	0.001 (sig.)
8	51	49	0.333	2.469	0.017 (sig.)	-0.422	-3.257	0.002 (sig.)
9	47	45	-0.110	-0.742	0.462	-0.237	-1.634	0.109
10	53	51	0.234	1.719	0.092	-0.300	-2.247	0.027 (sig.)
All	493	491	0.152	3.420	0.001 (sig.)	-0.179	-4.025	0.000 (sig.)

Overall and in four out of the ten simulations, the (positive) correlation r_{wcc} between *wcc* events and clonal success was significant. There was also a significant correlation between *mwr* events and clonal success overall and in six of the simulations, but the direction was negative, the opposite to that hypothesised. This latter result is counter-intuitive and will be investigated in a future paper since it requires analysis using other complex event types. As well as considering different simulations, we also carried out a correlation analysis for each clone in each simulation (these results are given in Appendix 2). Again, *wcc* events and *mwr* events correlated with clonal success on some occasions but not others. The differences in the t values for r_{wcc} and r_{mwr} (determining their significance) for the different simulations and clones implies that the same global effect (e.g. clonal success) can have different underlying mechanisms, even with the *same* agent-based model. The next step would be to determine which other mechanisms are at work and which mechanisms tend to correlate with one another. This can again be done through the specification and detection of complex event types.

5 Summary and conclusions

In this paper we have shown how the complex event formalism can be used to specify multi-level behaviours in agent-based simulations. These can differ in both scope and resolution. The identification of complex event types gives us a computational method for testing hypotheses about such behaviours, making simulations less ‘opaque’. We have demonstrated this by showing correlation relationships between global system behaviours and the interactive mechanisms at lower levels. By showing that correlation relationships can differ amongst different simulations, we have also shown that the same global system behaviour can have different underlying mechanisms, even with the same agent-based model. These multi-level interactive mechanisms are well worth investigating if we are to achieve an understanding of the system beyond simple individual-rule to global behaviour mapping.

Given that complex event types are composed of simple event types (which can be related directly to the agent rules), we have a means of determining which agent rules play a significant role in generating a particular higher level behaviour. Although this has not been discussed in detail in this paper, it is well worth pursuing, particularly if we wish to understand how interventions in a system can affect behaviour. Another promising avenue for further investigation is in the use of more sophisticated statistical methods such as causal state splitting [15] to determine the mechanisms that are critical for a particular higher level behaviour. The complex event formalism would allow us to apply such techniques to behaviours at any level.

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