The use of Agent-based Simulation to Discover Extreme Cases in Immune-Interactions with Early-Stage Cancer Scenarios

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Early-stage cancer and its interactions with the immune system are still not fully understood. In order to better understand these processes, researchers employ different methods. Simulation and in particular, agent-based simulation (ABS) have been found useful tools for understanding it (Look et al., 1981; Castiglione et al., 1999, 2001; Bonabeau, 2002; Figueredo and Aickelin, 2011; Figueredo et al., 2013a,b).

In a previous study (Figueredo et al., 2013b) we have built an ABS model to study the interplay of immune cells and early-stage cancer. The model considers interactions between tumour cells and immune effector cells, as well as the immune-stimulatory and suppressive cytokines IL-2 and TGF-β. IL-2 molecules mediate the immune response towards tumour cells. They interfere on the proliferation of effector cells according to the number of tumour cells in the system. Conversely, TGF-β stimulates tumour growth and suppresses the immune responses by inhibiting the activation of effector cells and reducing tumour-antigen expression.

In order to validate our model, we used a well-established mathematical model found in the literature (Arciero et al., 2004). While at average both models do not show a statistical significant difference, some additional trends in the results of the ABS model are observed. As ABS is a stochastic simulation method, it was run for multiple times. Instead of having one solution, as it is the case for a deterministic mathematical model, ABS produces a variety of outcomes. These solutions are usually very similar. In our cases study, however, we could observe some instances which could not have been observed by using analytical methods (see Figure 1).

The use of ABS modelling has therefore led to the discovery of additional "rare" patterns, which we would have not been able to derive by using analytical methods. These "extreme cases" indicate that there might be circumstances where the tumour cells are completely eliminated by the immune system, without the need of any cancer therapies. We strongly believe that the observed emergent behaviour produced by stochastic simulation can make a useful contribution to assisting immunological research. With the additional information supplied from the ABS, immunologists can test new hypotheses and further investigate whether these extreme cases actually occur in reality and why.

Currently, we are working on a methodology for defining experimental conditions that would allow us to observe similar emergent behaviour in other simulation experiments related to early-stage cancer research. One important aspect here is to investigate the statistical conditions under which emergent behaviour starts to appear. The questions we are looking at are:

1. How many replications of our stochastic simulation do we have to run before we can expect to see rare behaviours?
2. Is there any regularity in the growth of these rare emerging patterns?
3. What are the factors that need to be considered when predicting the occurrences of emerging patterns (e.g. level of dynamics in the model)?

The patterns obtained in our previous work were a result of 50 independent runs of the ABS model (Figueredo et al., 2013b). In order to further advance our knowledge regarding these patterns we are currently running experiments with 10,000 independent runs in order to verify whether there is any regularity in pattern growth. We also intend to validate our results with immunologists. It is hoped that the development of a methodology to further investigate extreme cases could assist in defining suitable vaccination strategies and the appropriateness of cancer treatments by the prediction of the possible outcome scenarios and how frequently they take place.

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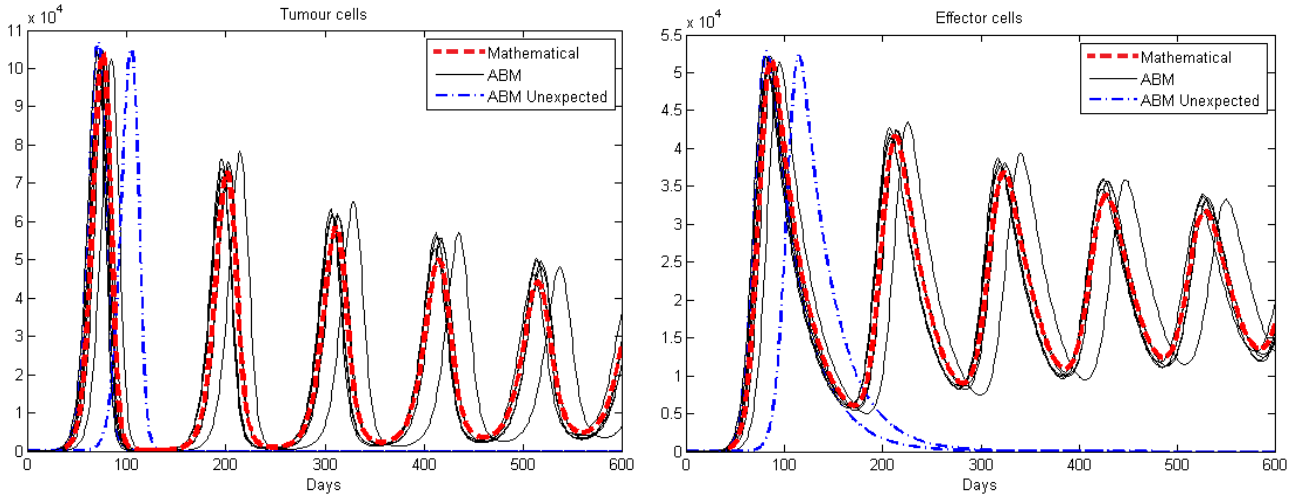

(a) Simulation results for tumour cells

(b) Simulation results for effector cells

Figure 1: Simulation results: the dashed line (red) shows the mathematical output; the lines in black show exemplar ABS results for 6 runs. As it can be seen, there are some results very close to the mathematical formulation and others presenting more variability due to the ABS stochastic behaviour. These variations, however, follow the same pathway as the analytical solution. The dashed-dotted line (blue) shows the rare cases determined by the ABS simulations.

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