Assignment 1 (PHYC90010)
To be handed in by the 10th of April (5pm)

A fascinating branch of research in the life sciences today is systems biology. Its practitioners seek to construct predictive, quantitative models of complex biological systems by modelling how the fundamental elements (e.g. cells) interact and communicate via metabolic and signalling networks. An outstanding question in this area, and a classic example of spatio-temporal pattern formation, is how tumours emerge naturally from the dynamics of the immune system's surveillance network. Phenomenological models for tumour growth abound. For example, Gompertz showed that the volume *V* of a tumour evolves with time *t* exponentially according to the law

$$V = V_0 \exp\left[\frac{A}{B}\left(1 - e^{-Bt}\right)\right],$$

where V_0 is the initial volume, and A and B are rate constants determined empirically. It is pertinent to ask whether such empirical laws can be derived theoretically from the underlying ordinary or partial differential equations describing the surveillance network dynamics.

In this question, we model the growth of tumours with a cellular automaton. We begin by following closely the classic work by Qi, Zheng, Du & An, Journal of Theoretical Biology **161**, 1 (1993).

Consider a simple model in which a piece of tissue is divided into a regular, square grid of compartments. At any instant, every compartment contains one of the following: a normal cell *N*, a cancerous cell *C*, a cytotoxic complex *E*, or a dead cancerous cell *D*. In addition, every compartment contains an effector E_0 which is dormant in the *N*, *C*, or *D* states and active in the *E* state. Effectors are the sentinels of the immune system's surveillance network. When activated, they bind to a cancerous cell and emit chemical signals that recruit other cytotoxic entities ("assassins") to the site. Macrophages, for example, are cytotoxic; they kill cells by engulfing and digesting them.

The myriad processes in the immune system can be reduced to the following simplified network.

$$N \to C \ \text{ rate } \ k_0, \quad (1)$$
$$C \to 2C \ \text{ rate } \ k_1', \quad (2)$$
$$C + E_0 \to E \ \text{ rate } \ k_2, \quad (3)$$
$$E \to E_0 + D \ \text{ rate } \ k_3, \quad (4)$$
$$D \to N \ \text{ rate } \ k_4. \quad (5)$$

Equation (1), which was not included by Qi *et al.* (1993), describes random mutations, which convert a normal cell into a cancerous one. Equation (2) describes the proliferation of the cancer, i.e. a cancerous cell "infects" one of its neighbours. Equations (3) and (4) describe the two-stage assassination of a cancerous cell: the effector binds to the cell and recruits assassins, forming a cytotoxic complex; then, its work done, the complex dissolves to leave behind a dead cancerous cell and dormant effector. Equation (5) describes dissolution of a dead cell and its replacement by a normal cell.

1. What plays the role of an external driver, analogous to the source of grains in a sand pile, in the system (1)–(5)? [1]
2. Write down a set of rules for a cellular automaton which implements (2)–(5), i.e. without mutations. State clearly how a compartment is updated at each time step when it occupies the *N*, *C*, *E*, or *D* state. The proliferation step (2) is limited by *C*-cell competition for the finite supply of nutrients *in vivo* (Qi et al. 1993). Include competition by setting the proliferation rate to

$$k_1' = k_1 \left(1 - \frac{q}{4}\right),$$

   where $q \leq 4$ is the number of *C*-cell neighbours. This approach is simpler than that prescribed by Qi et al. (1993). [5]
3. Implement the automaton in a computer programming language of your choice. Your automaton should be synchronous, meaning that every compartment is updated once per time step. [4] (**Note:** If you are having problems writing the code then let me know. I am happy to give you a basic code)
4. Starting with a few randomly situated *C* cells, run the automaton, until it reaches a statistically stationary state. Choose constant values of k_1, k_2, k_3 and k_4 from the ranges suggested in Table 1 of Qi et al. (1993), with k_1, k_3 and k_4 greater than k_2.
   i. Does the initial rise in tumour volume reproduce Gompertz's law? [1]
   ii. Why must we choose k_1, k_3 and k_4 to be greater than k_2? [2]
   iii. By running many realisations of the automaton, starting with the same number of *C* cells each time, plot $p(x_c)$, the probability density function (PDF) of x_c, the total number of *C* cells in the stationary state. Comment on its shape. [3]
   iv. Compute the variance $\mathrm{var}\{x_c\}$. Interpret your answer in terms of the central limit theorem. [3]
   v. Derive analytically the mean number of *C*, *E*, and *D* cells in the stationary state? (Hint: $\langle x_c \rangle \approx 1\text{-}k_2/k_1$) [5]
6. Now switch off competition among proliferating *C* cells ($k_1' = k_1$) and take $k_1 = k_2$, so that cytotoxicity balances proliferation. Run many realisations of the automaton, starting with the same number of *C* cells. Plot the PDF $p(x_c)$ after a fixed, sensibly chosen number of iterations. Comment on its shape. [3]

7. Switch on mutations [Equation (1)] while keeping $k_1' = k_1 = k_2$ and plot $p(x_c)$.
   i. Show that the system approaches a stationary state, where x_c is independent of k_0. In this respect, the system resembles a sand pile, whose mean angle of repose does not depend on the rate at which grains are added. [2]
   ii. (**Optional**) Can you derive analytically the mean number of C, E, and D cells in the stationary state? [Hint: $\langle x_c \rangle \approx (1+k_2/k_3+k_2/k_4)^{-1}$]
   iii. Do you see evidence for avalanches in $p(x_c)$, when the mutations are fast ($k_0 \gg k_1$) or slow ($k_0 \ll k_1$)? [3]
8. Switch on competition again. Can you tune k_1, k_2, k_3 and k_4 to get avalanches and a power-law PDF? [3]
9. Suppose C cells develop defences against effectors; for example, another cell type V ("virus") may deactivate E_0 in neighbouring compartments, or the C cells themselves may deactivate E_0 if enough of them cluster together. Experiment with these ideas. Demonstrate a defence mechanism that lets the tumour grow despite processes (3) and (4). Then propose a new immune response which defeats the defence mechanism in an interesting way. (Maybe the E complexes proliferate, or an "anti-virus" intervenes?) Explain your new rules clearly, plot some relevant PDFs, and discuss the results in terms of non-equilibrium statistics. (Needless to say, there is no single correct answer here.) The immune system that protects an organism today, and the diseases to which it remains vulnerable, have co-evolved through many cycles of defence and counter-attack over millions of years, in the context of natural selection. [5]

Total Marks 40