Agent-based modelling of viral infection

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The three phases of the macroscopic evolution of the HIV infection are well-known, but it is still difficult to understand how the cellular-level interactions come together to create this characteristic pattern and in particular why there are such differences in individual responses. An "agent-based" approach is chosen, as a means of inferring high-level behaviour from a small set of interaction rules at the cellular level. Here the emphasis is put on the cell mobility and the viral mutations.

One of the most characteristic aspects of the HIV infection is its evolution: first in the short acute phase, the original viral strains are destroyed, in the second year-long latency period, the number of strains slowly increases and, in the final phase, the acquired Immunodeficiency syndrome, (AIDS), develops when the immune system is no longer able to cope with the multiplying strains and is overcome. The principal aim of this work, based at Dublin City University, is to try to understand why the range of experience with respect to HIV infection is so diverse. In particular, the work aims to address questions relating to variation in length in individual latency period. This may be very long, (for relatively low success of antipathetic mutation), in one individual, compared to another with much higher mutation levels.

The indications are that the observed variation lies in the priming and initial level of fitness of the immune response of the individual, together with the various factors influencing this. If such "priming patterns" can be recognised, or even predicted, then in the long term we may have a way of "typing" an individual and targeting intervention appropriately. Unfortunately, understanding how the immune system is primed by experience of antigenic invasion and diversity is non-trivial. The challenge is to determine what assumptions can be made about the nature of the experience, can be modelled, tested against clinical data and hence argued plausibly. The aim is to understand how the cell interactions lead to the observed endpoints. What exactly is involved in antigenic diversity? How variable is the mutation rate and the viral load? What is the importance of cell mobility and how realistic is this in terms of cross-infection and sub-system involvement? How important then is the cross-reactivity?

The immune response is dynamic and includes growth and replenishment of cells and in-built adaptability, through mutation of its defences to meet new threats. It also includes aspects of cell mobility, which may be captured, by means of defining movement and affinity of cell-types in a defined spatial framework. In particular, this will enable study of variation in viral load and the way in which host response may lead to degradation of protection.

To investigate these questions, an "agent-based" approach is chosen, as a means of inferring high-level behaviour from a small set of interaction rules at the cellular level. Such behaviour cannot be extracted analytically from the set of rules, but emerge as a result of stochastic events, which play an important part in the immune response.

The initial model consists of agents, (or functional units), with designated properties which mimic the operation of a single lymph node; (as a test case). This prototype, however, includes all known interactions contributing to cell-mediated immunity and the local evolution of the virions. The antibody-mediated response has not been considered initially, because the cell-mediated arm plays a dominant role in repelling attack. The agents implemented represent Th (helper) and Tc (cytotoxic) lymphocytes, Antigen Presenting Cells, and virions. They inherit from a common C++ class

designed to deal with features such as the mobility. Then each class implements through attributes and methods the specific properties of each cell type, such as the activation of a Tc cell by a Th cell. The lymph node is modelled as a matrix in which each element is a physical neighbourhood able to contain various agents of each type.

The next step is to increase of the number of lymph nodes. This extension involves millions of agents and requires major computational effort, so that parallelisation methods are inevitable. The use of these methods is a natural consequence and advantage of the multi-agent approach. A human body contains hundreds of lymph nodes. The aim is here to extend the size and complexity of the systems that can be modelled to something approaching realism.

The representation of the *innate* response as a common background and the *adaptive* part as a characterised set of features will be the next step to looking at progression of a large system over a longer period in order to focus on disease progression endpoints and intervention effects.

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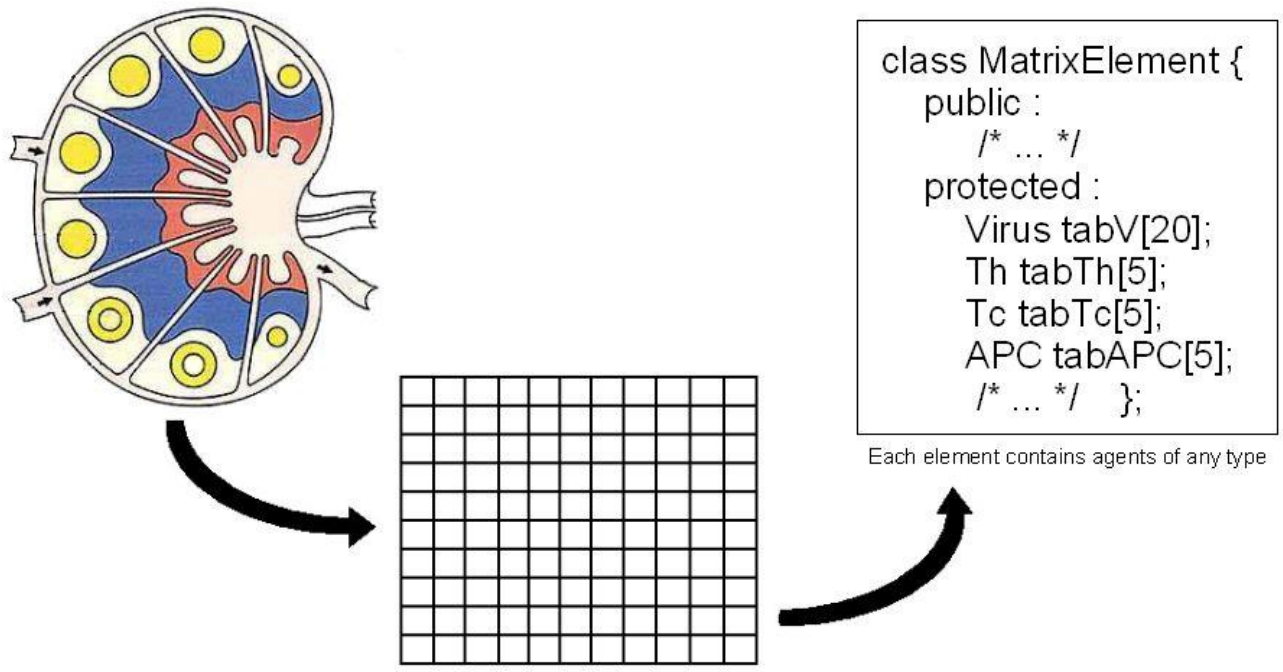

The lymph node (adapted from N. Levy, Pathology of lymph nodes, 1996) is modelled as a matrix in which each element is a physical neighbourhood and can contain several agents of each type.

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